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(71) Applicant *(for all designated States except US)*: **THE PENN STATE RESEARCH FOUNDATION** [US/US]; 113 Technology Center, University Park, PA 16802-7000 (US).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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WO 02/044184 A3

(54) Title: DNA METHYL TRANSFERASE INHIBITORS

(57) Abstract: This invention provides broad-spectrum antibiotics that are inhibitors of bacterial adenine DNA methyltransferases.

INTERNATIONAL SEARCH REPORT

Ir tional Application No
PCT/US 01/45129

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F5/02 C07B61/00 A61K33/22 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F C07B A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 485 864 A (BIRNBAUM HERMAN A ET AL) 23 December 1969 (1969-12-23). column 8, line 10 - line 20	1,2
X	column 8, line 12	2
X	FR 2 071 171 A (RHONE POULENC SA) 17 September 1971 (1971-09-17) page 4 -page 10; examples 1-14 page 2; figure III	1
X	US 4 713 346 A (FLUECKIGER RUDOLF ET AL) 15 December 1987 (1987-12-15) column 12, line 12; table 1	1
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2002	05/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bader, K

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 44387 A (FUJIKAWA MASAZUMI ;HAYASE YOSHIO (JP); SHIONOGI & CO (JP); IMAZAKI) 3 August 2000 (2000-08-03) page 3 page 4 page 37	1,2
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HOHAUS, EBERHARD ET AL: "Mass spectrometric studies on boron chelates. Part IV. Fragmentations of diphenylboron chelates and monophenylboron chelates - mixture analysis" retrieved from STN Database accession no. 91:174350 XP002209944 abstract & INT. J. MASS SPECTROM. ION PHYS. (1979), 31(1-2), 113-23 ,	1,2
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YUAN, GUOZHENG ET AL: "Ligand substitution reaction of diarylboron chelates" retrieved from STN Database accession no. 114:207314 XP002209945 abstract & WUJI HUAXUE XUEBAO (1990), 6(3), 314-18 ,	1,2
X	DE 198 29 949 A (BAYER AG) 5 January 2000 (2000-01-05) page 16 -page 21	1
X	HOHAUS ET AL: "Boron chelates and boron metal chelates. I. Boron chelates with chelating agents of the pyridine and quinoline series and their N-oxides" CHEMISCHE BERICHTE, VERLAG CHEMIE GMBH. WEINHEIM, DE, vol. 102, 1969, pages 4025-4031, XP002127342 ISSN: 0009-2940 page 4028	1

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INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/US 01/45129

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 75142 A (WALL MARK ;BAKER STEPHEN J (US); SHAPIRO LUCILLE (US); WAHNON DAPH) 14 December 2000 (2000-12-14) page 5, line 21 - line 24 page 7, line 12 - line 31 page 35, line 1 - line 5 page 42, line 5 -page 46, line 12 page 50, line 13 - line 20	1-9

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/45129

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4-7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1,3-9
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,3-9

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to compounds according to claim 1 wherein the substituents are as defined in the two tables depicted on page 18 of the description, line 1- line 5. The compounds according to claim 2 have been searched in full.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3485864 A	23-12-1969	NONE	
FR 2071171 A	17-09-1971	FR 2071171 A6	17-09-1971
US 4713346 A	15-12-1987	NONE	
WO 0044387 A	03-08-2000	EP 1155698 A1	21-11-2001
		WO 0044387 A1	03-08-2000
DE 19829949 A	05-01-2000	EP 1074602 A1	07-02-2001
		DE 19829949 A1	05-01-2000
		JP 2000138096 A	16-05-2000
		US 2002006528 A1	17-01-2002
WO 0075142 A	14-12-2000	AU 7569800 A	28-12-2000
		EP 1181291 A2	27-02-2002
		WO 0075142 A2	14-12-2000

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(74) Agent: **NOONAN, Kevin, E.**; McDonnell Boehnen Hulbert & Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

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WO 02/44184 A2

(54) Title: DNA METHYL TRANSFERASE INHIBITORS

(57) Abstract: This invention provides broad-spectrum antibiotics that are inhibitors of bacterial adenine DNA methyltransferases.

DNA METHYL TRANSFERASE INHIBITORS

This application is related to U.S. Serial No. 09/578,991, filed May 25, 2000, which claims priority to U.S. Provisional applications Serial Nos. 60/135,870, filed May 25, 1999; 60/154,582, filed September 17, 1999; and 60/174,256, filed January 3, 2000, the disclosures of each of which are incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the field of antibiotics and particularly antibacterial compounds. The invention specifically relates to antibiotics targeted to DNA modification enzymes, in particular adenine DNA methyltransferases, that are the components of a broad variety of different bacterial pathogens including those that are essential for bacterial cell growth. The invention particularly provides inhibitors of such adenine DNA methyltransferases having little or no inhibitory effects on cytosine methyltransferases, and hence having limited effects on eukaryotic, particularly mammalian, cells. Methods for preparing and using the adenine DNA methyltransferase inhibitors of the invention, and pharmaceutical compositions thereof, are also provided.

2. Background of the Invention

One hallmark of the modern era of medicine has been the decline in morbidity and mortality associated with bacterial infections. The development of a variety of antibiotic drugs in the early and middle parts of the twentieth century provided medical practitioners for the first time with effective treatments for a variety of infectious diseases.

However, misuse of conventional antibiotics and natural selection of the infectious bacterial population has resulted in the development of varying degrees of drug resistance by most bacterial infectious agents to most antibiotic agents. In severe cases, such as MRSA (Multidrug-Resistant StaphA), one or only a few antibiotics are currently effective. In addition, the existence of immunodeficiency syndromes results in additional incidence of opportunistic infections requiring intensive antibiotic treatment.

Thus, there is an increasing need in the art for novel, more effective antibiotic compounds for treating bacterial infections that are resistant to currently available therapies.

Most bacteria modify their genomic DNA by methylation of specific nucleotide bases. DNA methylation is critical to gene regulation and repair of mutational lesions (*see* Jost & Soluz, 1993, DNA METHYLATION, MOLECULAR BIOLOGY AND BIOLOGICAL SIGNIFICANCE, Birhauser Verlag: Basel, Switzerland; Palmer & Marinus, 1994, *Gene* 143: 1-12; Dryden, 1999, "Bacterial DNA Methyltransferases," in S-ADENOSYLMETHIONINE-DEPENDENT METHYLTRANSFERASES: STRUCTURES AND FUNCTIONS, X. Cheng and R. M. Blumenthal (eds.), World Scientific Publishing, p.283-340 *for review*). DNA methylation is catalyzed by a class of enzymes having different sequences specificities. There are those DNA methyltransferases for example (*dam*) that methylate adenine residues in GATC sequences, or cytosine (*dcm*) residues in CCAGG or CCTGG sequences that are not contained in the recognition site of a cognate restriction enzyme. There are those DNA methyltransferases that methylate residues contained in the recognition site of a cognate restriction enzyme (*for example, Apa*I, *Ava*II, *Bcl*I, *Cla*I, *Dpn*II, *Eco*RI, *Hae*III, *Hha*I, *Mbo*I, and *Msp*I; *see*, Marinus & Morris, 1973, *J. Bacteriol.* 114: 1143-1150; May & Hatman, 1975, *J. Bacteriol.* 123: 768-770; Heitman, 1993, *Genet. Eng.* 15: 57-108). In addition, the instant inventors have discovered an adenine DNA methyltransferase from *Caulobacter cresentus* that methylates the adenine residue in the sequence GANTC, as disclosed in International Application Publication No. WO98/12206. This methyltransferase is cell-cycle regulated and essential for successful bacterial cell growth; inhibition of the enzyme makes the bacteria non-viable. Similar methyltransferases have also been discovered in *Brucella abortus*, *Helicobacter pylori*, *Agrobacterium tumefaciens* and *Rhizobium meliloti*. In contrast with bacterial cells, DNA methylation in eukaryotic, and particularly mammalian cells, is limited to cytosine methylation at sites comprising the sequence CpG (Razin & Riggs, 1980, *Science* 210: 604-610; Jost & Bruhat, 1997, *Prog. Nucleic Acid Res. Molec. Biol.* 57: 217-248).

Thus, the existence of DNA methylation, in particular, the cell-cycle regulated adenine DNA methyltransferase found by the inventors in certain

bacterial species, addresses the need in the art for novel targets for antibiotic activity.

SUMMARY OF THE INVENTION

The invention provides antibiotic compounds capable of inhibiting adenine DNA methyltransferases in bacterial cells. The antibiotic compounds of the invention specifically inhibit adenine-specific bacterial DNA methyltransferases, and do not inhibit bacterial or eukaryotic, particularly mammalian and most particularly human, cytosine-specific DNA methyltransferases. The compounds of the invention also inhibit adenine-specific DNA methyltransferases in plants. The antibiotic compounds are also provided as pharmaceutical compositions capable of being administered to an animal, most preferably a human, for treatment of a disease having a bacterial etiology, or an opportunistic infection with a bacteria in an animal, most preferably a human, in an immunologically compromised or debilitated state of health.

The invention also provides methods for preparing the antibiotic compounds and pharmaceutical compositions thereof, and methods of using said antibiotics therapeutically. Kits and packaged embodiments of the antibiotic compounds and pharmaceutical compositions of the invention are also provided.

Specific preferred embodiments of the present invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention provides antibiotics, and specifically antibacterial compounds, that are inhibitors of bacterial adenine DNA methyltransferases. The compounds of the invention exhibit antibacterial, growth-inhibitory properties against any bacterial species that produces an adenine DNA methyltransferase. These include adenine DNA methyltransferases that are components of bacterial restriction/modification systems as understood in the art, as well as cell-cycle regulated adenine DNA methyltransferases (CcrM), such as those disclosed in International Application Publication No. WO98/12206, incorporated by reference.

Thus, inhibitors of adenine DNA methyltransferases are particularly provided by the invention.

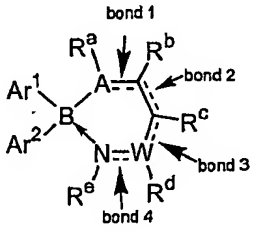
The adenine DNA methyltransferase inhibitors of the invention comprise a novel class of broad-spectrum antibiotics. Most bacterial species possess a DNA methyltransferase that is part of a modification apparatus, typically associated with a restriction enzyme, that preserves the integrity of cellular DNA while providing a defense against foreign (most typically viral) DNA. In addition, certain bacteria produce an adenine DNA methyltransferase that is essential for bacterial cell growth. Medically-important bacterial species that provide appropriate targets for the antibacterial activity of the inhibitors of the invention include gram-positive bacteria, including cocci such as *Staphylococcus* species and *Streptococcus* species; bacilli, including *Bacillus* species, *Corynebacterium* species and *Clostridium* species; filamentous bacteria, including *Actinomyces* species and *Streptomyces* species; gram-negative bacteria, including cocci such as *Neisseria* species; bacilli, such as *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Hemophilus* species, *Pasteurella* species, and *Streptobacillus* species; spirochetal species, *Campylobacter* species, *Vibrio* species; and intracellular bacteria including *Rickettsiae* species and *Chlamydia* species.

Specific bacterial species that are targets for the adenine DNA methyltransferase inhibitors of the invention include *Staphylococcus aureus*; *Staphylococcus saprophyticus*; *Streptococcus pyrogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Bacillus anthracis*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *Neisseria gonorrhoeae*; *Neisseria meningitidis*; *Pseudomonas aeruginosa*; *Legionella pneumophila*; *Escherichia coli*; *Yersinia pestis*; *Hemophilus influenzae*; *Helicobacter pylori*; *Campylobacter fetus*; *Vibrio cholerae*; *Vibrio parahemolyticus*; *Trepomena pallidum*; *Actinomyces israelii*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus* and *Agrobacterium tumefaciens*.

It is an important property of the adenine DNA methyltransferase inhibitors of the invention that the level of activity of these substances with cytosine-specific DNA methyltransferases is low. This is because cytosine-specific DNA

methyltransferases occur in mammalian, most particularly human, cells, and it is an advantageous property of the adenine DNA methyltransferases of the invention to have little or no inhibitory activity against mammalian methyltransferases. This property confers upon the molecules provided by the invention the beneficial property of being bacterial cell specific, and having little antibiotic activity against mammalian, most preferably human, cells. Preferably, the IC_{50} of these compounds for cytosine-specific DNA methyltransferases is greater than 500μM.

The invention also provides compounds of Formula I:



or a pharmaceutically acceptable salt thereof,

wherein A is N, O or S;

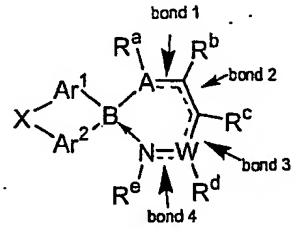
W is C_p, where p is 0 or 1;

R^a, R^b, R^c, R^d, and R^e are the same or different and are independently hydrogen, halogen, nitro, nitroso, lower alkyl, aryl or substituted aryl, lower alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl or cycloalkyl group is optionally substituted with halogen, lower alkyl or lower alkoxy, aryl or substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, ester, or sulfate, or wherein R^a, R^b, R^c, R^d, and R^e may be connected by aromatic, aliphatic, heteroaromatic, heteroaliphatic ring structures or substituted embodiments thereof, where R^a is absent when A is O or S and R^d is absent when p = 0; and

wherein Ar^1 and Ar^2 can be the same or different and are each independently aryl or aryl substituted at one or a plurality of positions with halogen, nitro, nitroso, lower alkyl, aryl or substituted aryl, lower

alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl or cycloalkyl group is optionally substituted with halogen, lower alkyl or lower alkoxy, aryl or substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, ester, or sulfate, and

optionally Ar1 and Ar2 maybe cojoined to create a tricyclic scaffold (vide infra), where X = C=O, CHOH, $(CH_2)_n$ (n = 0 to 2), -CH=CH-, NR^f (R^f = H, C_1-C_4 alkyl, phenyl, thienyl, or pyridyl), O, SO_n (n = 0 to 2), which have a plurality of positions with halogen, nitro, nitroso, lower alkyl, aryl or substituted aryl, lower alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and



wherein bond 1, bond 2, bond 3 and bond 4 are independently a single bond or a double bond, provided that when A is S or O, bind 1 is a single bond and where A is N, bond 1 is a double bond..

Thus, the invention provides adenine DNA methyltransferase inhibitors that are derivatives of borinic acid, most preferably diphenyl or substituted diphenyl borinic acid, and most preferably diphenyl or substituted diphenyl borinic acid alkylamine esters thereof. In preferred embodiments, the invention provides compounds including di-(4-fluorophenyl)borinic acid 8-hydroxyquinoline ester, di-(4-chlorophenyl)borinic acid 8-hydroxyquinoline ester, di-(3-chlorophenyl)borinic acid 8-hydroxyquinoline ester, di-(4-chloro-2-fluorophenyl)borinic acid 8-

hydroxyquinoline ester, di-(3,4-methylenedioxyphenyl)borinic acid 8-hydroxyquinoline ester, di-(4-methoxyphenyl)borinic acid 8-hydroxyquinoline ester, di-(2-thienyl)borinic acid 8-hydroxyquinoline ester, di-(p-fluorophenyl)borinic acid 8-hydroxyquinaldine ester, di-(p-chlorophenyl)borinic acid 8-hydroxyquinaldine ester, di-(4-methoxyphenyl)borinic acid 8-hydroxyquinaldine ester, di-(p-fluorophenyl)borinic acid 5-chloro-8-hydroxyquinaline ester, di-(p-chlorophenyl)borinic acid 5-chloro-8-hydroxyquinaline ester, di-(3,4-methylenedioxyphenyl) borinic acid 5-chloro-8-hydroxyquinoline ester, di-(4-methoxyphenyl)borinic acid 5-chloro-8-hydroxyquinoline ester, di-(3,4-methylenedioxyphenyl)borinic acid 8-hydroxy-5-nitroquinoline ester, diphenylborinic acid 2-aminophenol, diphenylborinic acid pyridine-2-methanol, diphenylborinic acid 2-amino-1-phenylpropanol, diphenylborinic acid (S)-(+)-pyrrolidine-2-methanol, di-(4-fluorophenyl)borinic acid ethanolamine ester, and di-(4-chlorophenyl)borinic acid ethanolamine ester.

In certain situations, compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, *i.e.*, optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Regardless of how a putative adenine DNA methyltransferase is prepared according to the invention, the compound is analyzed for both adenine and cytosine-specific DNA methyltransferase activity. Susceptible bacteria (known to express an adenine DNA methyltransferase) are grown in the presence and absence of the inhibitory compound, and the extent of growth inhibition in the presence of the compound is determined relative to growth in the absence of the compound. The mechanism of action (*i.e.*, inhibition of adenine DNA methyltransferase) is verified for each growth-inhibitory compound by filter-binding radioassay using hemimethylated DNA, tritiated *S*-adenosyl methionine (C^3H_3) and a purified adenine DNA methyltransferase according to International Application Publication No. WO98/12206.

Compounds of the invention can exist as tautomers in solution. When structures and names are given for one tautomeric form the other tautomeric form is also included in the invention.

Representative compounds of the present invention include, but are not limited to the compounds disclosed herein and their pharmaceutically acceptable acid and base addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

The present invention also encompasses the acylated prodrugs of the compounds of the invention. Those skilled in the are will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the inventive compounds.

By "alkyl", "lower alkyl", and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkoxy", "lower alkoxy", and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "cycloalkyl", e.g., C_3-C_7 cycloalkyl, in the present invention is meant cycloalkyl groups having 3-7 atoms such as, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. In the C_3-C_7 cycloalkyl groups, preferably in the C_5-C_7 cycloalkyl groups, one or two of the carbon atoms forming the ring can optionally be replaced with a hetero atom, such as sulfur, oxygen or nitrogen. Examples of such groups are piperidinyl, piperazinyl, morpholinyl,

pyrrolidinyl, imidazolidinyl, oxazolidinyl, azaperhydroepinyl, oxazaperhydroepinyl, oxepanyl, oxazaperhydroinyl, and oxadiazaperhydroinyl. C_3 and C_4 cycloalkyl groups having a member replaced by nitrogen or oxygen include aziridinyl, azetidinyl, oxetanyl, and oxiranyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy. Preferred aryl groups include phenyl and naphthyl, each of which is optionally substituted as defined herein.

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, pyridyl, pyrimidinyl, (iso)quinolinyl, napthyridinyl, benzimidazolyl, benzoxazolyl. Preferred heteroaryls are thiazolyl, pyrimidinyl, preferrably pyrimidin-2-yl, and pyridyl. Other preferred heteroaryl groups include 1-imidazolyl, 2-thienyl, 1-, or 2- quinolinyl, 1-, or 2- isoquinolinyl, 1-, or 2- tetrahydro isoquinolinyl, 2- or 3- furanyl and 2- tetrahydrofuranyl.

The bacterial growth inhibitory, adenine DNA methyltransferase inhibiting compounds of the invention are provided as described herein.

Uses of the Compounds of the Invention

The invention also provides embodiments of the compounds disclosed herein as pharmaceutical compositions. The pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, *e.g.*, by means of a conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitic, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

For injection, the compounds of the invention can be formulated in appropriate aqueous solutions, such as physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal and transcutaneous administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents

that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use. The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system can be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system can be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components can be varied: for example, other low-toxicity nonpolar surfactants can be used instead of polysorbate 80; the fraction size of polyethylene glycol can be varied; other biocompatible polymers can replace polyethylene glycol, *e.g.* polyvinyl pyrrolidone; and other sugars or polysaccharides can substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also can be employed, although usually at the cost of greater toxicity. Additionally, the compounds can be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers

containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein and nucleic acid stabilization can be employed.

The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

The compounds of the invention can be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, phosphoric, hydrobromic, sulfinic, formic, toluenesulfonic, methanesulfonic, nitic, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Pharmaceutical compositions of the compounds of the present invention can be formulated and administered through a variety of means, including systemic, localized, or topical administration. Techniques for formulation and administration can be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA. The mode of administration can be selected to maximize delivery to a desired target site in the body. Suitable routes of administration can, for example, include oral, rectal, transmucosal, transcutaneous, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one can administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a specific tissue, often in a depot or sustained release formulation.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays, as disclosed herein. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC50 (effective dose for 50% increase) as determined in cell culture, *i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of bacterial cell growth. Such information can be used to more accurately determine useful doses in humans.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination, the severity of the particular disease undergoing therapy and the judgment of the prescribing physician.

For administration to non-human animals, the drug or a pharmaceutical composition containing the drug may also be added to the animal feed or drinking water. It will be convenient to formulate animal feed and drinking water products with a predetermined dose of the drug so that the animal takes in an appropriate quantity of the drug along with its diet. It will also be convenient to add a premix containing the drug to the feed or drinking water approximately immediately prior to consumption by the animal.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by

Oravcová *et al.* (1996, *J. Chromat. B* 677: 1-27). Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD50 and ED50. Compounds that exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See, e.g.* Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch.1, p.1).

Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety that are sufficient to maintain bacterial cell growth inhibitory effects. Usual patient dosages for systemic administration range from 100 - 2000 mg/day. Stated in terms of patient body surface areas, usual dosages range from 50 - 910 mg/m^2/day. Usual average plasma levels should be maintained within 0.1-1000 μM. In cases of local administration or selective uptake, the effective local concentration of the compound cannot be related to plasma concentration.

The compounds of the invention are modulators of cellular processes in bacteria that infect plants, animals and humans. The pharmaceutical compositions of the adenine DNA methyltransferase inhibitory compounds of the invention are useful as antibiotics for the treatment of diseases of both animals and humans, including but not limited to actinomycosis, anthrax, bacterial dysentery, botulism, brucellosis, cellulitis, cholera, conjunctivitis, cystitis, diphtheria, bacterial endocarditis, epiglottitis, gastroenteritis, glanders, gonorrhea, Legionnaire's

disease, leptospirosis, bacterial meningitis, plague, bacterial pneumonia, puerperal sepsis, rheumatic fever, Rocky Mountain spotted fever, scarlet fever, streptococcal pharyngitis, syphilis, tetanus, tularemia, typhoid fever, typhus, and pertussis.

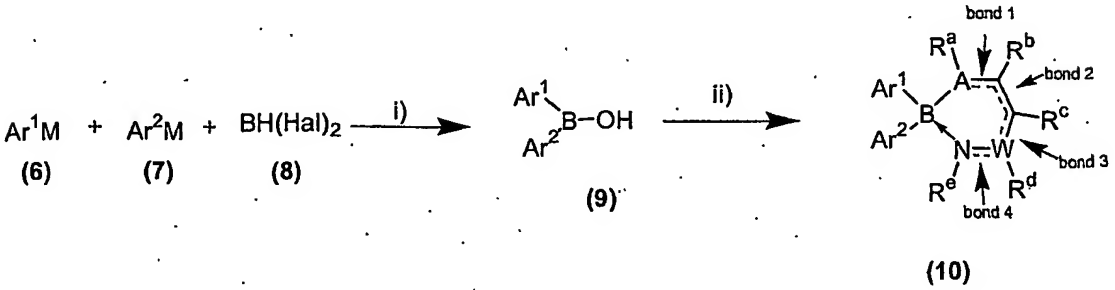
The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The following Examples are provided for the purposes of illustration and are not intended to limit the scope of the present invention. The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of individual aspects of the invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

EXAMPLE 1
Compounds based on Diphenyl Borinic Esters

Several compounds based on diphenyl borinic ester were prepared as follows. The general synthesis of these compounds is shown in Reaction Scheme 1.

Reaction Scheme 1



where the reaction conditions are:

i) tetrahydrofuran (THF) or ethyl ether (Et_2O), -78 °C to room temperature overnight;

ii) EtOH, room temperature, boron coordinating agent;

and where M = MgBr, Li

Hal = Cl, Br

A = O, N, S

W = C_p where p = 0,1

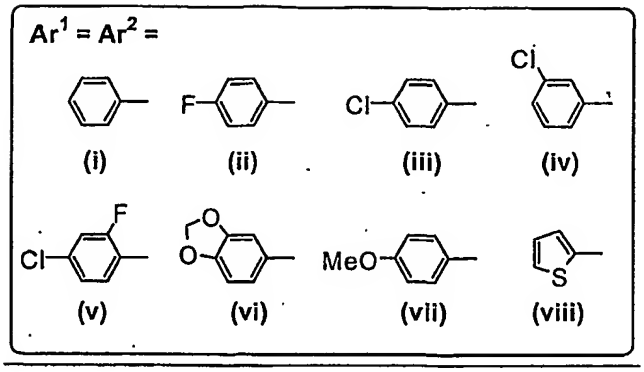
R^a, R^b, R^c, R^d, and R^e are the same or different and are independently hydrogen, halogen, nitro, nitroso, lower alkyl, aryl or substituted aryl, lower alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl or cycloalkyl group is optionally substituted with halogen, lower alkyl or lower alkoxy, aryl or substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, ester, or sulfate, or wherein R^a, R^b, R^c, R^d, and R^e may be connected by aromatic, aliphatic, heteroaromatic, heteroaliphatic ring structures or substituted embodiments thereof; where R^a is absent when A is O or S and R^d is absent when p = 0

bond 2, bond 3 and bond 4 are independently a single or a double bond; and when A = O, S, bond 1 is a single bond and when A = N, bond 1 is a single or a double bond

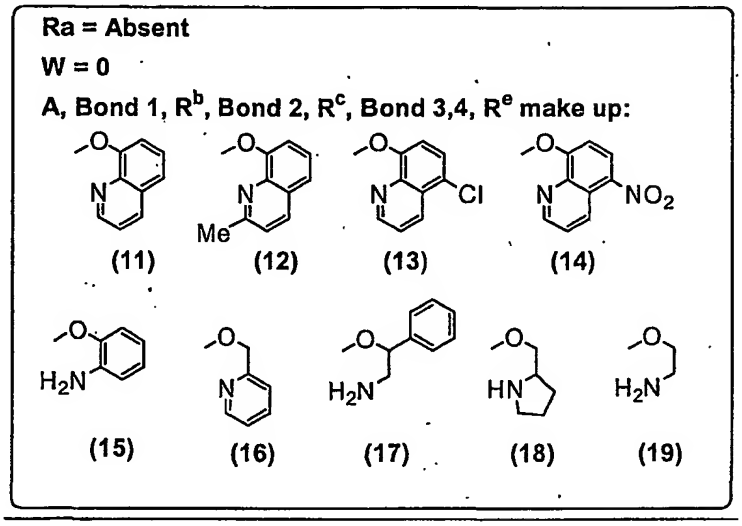
and

X can represent up to 5 substituents on each phenyl group, which can be independently hydrogen, lower alkyl, aryl or substituted aryl, lower alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from oxygen and nitrogen, and where any member of the alkyl, aryl or cycloalkyl group is optionally substituted with halogen, lower alkyl or lower alkoxy, aryl or substituted aryl, halide, nitro, nitroso, aldehyde, carboxylic acid, esters, amides, or sulfates.

Preferred compounds are identified herein based on the identity of the substituents $Ar^1 = Ar^2$ where:



are in combination with any one of the following:



General Experimental Protocols

Chemicals were purchased from Acros Organics and Aldrich Chemical Company (Milwaukee, WI) and were used without further purification. Tetrahydrofuran was dried by distillation from sodium and benzophenone; diethyl ether was dried over sodium and distilled; all other solvents used were the highest available grade and used without further purification.

Reactions were performed as set forth in detail below. Reaction products were analyzed by ^{1}H-NMR spectra recorded on a Bruker Avance 400 (400 MHz) and Bruker AMX360 (360 MHz). MALDI mass spectra were obtained using a Perspective Biosystems Voyager-DE STR, FAB mass spectra were obtained using a Kratos Analytical MS-50 TC, and APCI mass spectra were recorded on a Perspective Biosystems Mariner. Microanalyses were recorded by Atlantic Microlab Inc. (Norcross, Georgia 30091). Analytical thin layer chromatography

(tlc) was performed with Whatman silica gel aluminum backed plates of thickness 250 μm and fluorescent at 254 nm, and by using the solvent systems indicated. Flash column chromatography was performed with Selecto Scientific silica gel, 32-64 μm particle size. Melting points were obtained using a Mel-Temp II melting point apparatus with a Fluke K1 K/J type thermocouple digital thermometer and are uncorrected. Purity was determined by HPLC using a betabasic-18 (4.6 mm x 15 cm) column from Keystone Scientific Inc. and product eluted using a linear gradient of 0 to 40 % acetonitrile in 10 mM triethyl ammonium acetate over 20 mins.

Caulobacter crescentus strain CB15N was a gift from Prof. Lucille Shapiro, Department of Developmental Biology, Stanford University, Stanford, CA 94305, USA. *Bacillus subtilis* (ATCC #33234) was obtained from ATCC, Manassas, VA.

General methods for the synthesis of diaryl borinic acids (9)

Method A: Dichloroborane dimethyl sulfide complex or dibromoborane dimethyl sulfide (1 molar equivalent) was added to either tetrahydrofuran (0.2 mmol/mL) or diethyl ether (0.2 mmol/mL) under argon and cooled to -78°C. The aryl magnesium bromide (2 molar equivalents), in tetrahydrofuran, diethyl ether, cyclohexane, toluene or mixtures of these solvents, was added dropwise to the cold reaction mixture. The reaction was allowed to warm to room temperature and stirred overnight. The solvents were removed *in vacuo* and the residue was dissolved in diethyl ether. The reaction was stirred rapidly and hydrolyzed by the slow addition of 1N hydrochloric acid. Stirring was discontinued, the layers were separated and the organic layer was washed with saturated aqueous NaCl. The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an oil. This oil was dissolved in ethanol to an estimated concentration of 1M and divided into portions to be used in the subsequent precipitation with the various complexing agents.

Method B: Dichloroborane dimethyl sulfide complex or dibromoborane dimethyl sulfide complex (1 molar equivalent) was added to either tetrahydrofuran (2 mmol/mL) or diethyl ether (2 mmol/mL) under argon and cooled to -78°C. The

aryl lithium (2 molar equivalents), in tetrahydrofuran, diethyl ether, cyclohexane or mixtures of these solvents, was added dropwise to the cold reaction mixture. The reaction was allowed to warm to room temperature and stirred overnight. The solvents were removed *in vacuo* and the residue was dissolved in diethyl ether. The reaction mixture was stirred rapidly and hydrolyzed by the slow addition of 1N hydrochloric acid. Stirring was discontinued, the layers were separated and the organic layer was washed with saturated aqueous NaCl. The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an oil. This oil was dissolved in ethanol to an estimated concentration of 1M and divided into portions to be used in the subsequent precipitation with the various complexing agents.

Products are identified herein as a combination of the constituents identified above. Thus, di-(4-fluorophenyl)borinic acid 8-hydroxyquinoline ester is identified as **11ii**, indicating that $Ar^1 = Ar^2$ and are each 4-fluorophenyl (substituent **11** above), and R^a is absent, p = 0, and A, bond 1, R^b, bond 2, R^c, bond 3, bond 4 and R^e make up hydroxyquinoline (substituent **ii** above).

Di-(4-fluorophenyl)borinic acid 8-hydroxyquinoline ester (11ii): Di-(4-fluorophenyl)borinic acid was prepared using method A and was treated with 8-hydroxyquinoline (0.5M solution in ethanol). A yellow precipitate formed immediately and was collected by filtration and washed with ethanol. The product had the following properties upon analysis: mp 166-167°C; ^{1}H-NMR (360 MHz, C^2HCl_3,): δ 8.53 (d, J = 5.1 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 8.2, 7.7 Hz, 1H), 7.66 (dd, J = 8.2, 5.1 Hz, 1H), 7.39 (dd, J = 8.8, 6.7 Hz, 4H), 7.30 (d, J = 8.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 8.8 Hz, 4H); MS (+ve APCI) m/z 345 ($[M+H]^+$, ^{10}B), 346 ($[M+H]^+$, ^{11}B), 368 ($[M+Na]^+$, ^{11}B); Anal. ($C_{21}H_{14}NOBF_2$) C, H, N.

Di-(4-chlorophenyl)borinic acid 8-hydroxyquinoline ester (11iii): Di-(4-chlorophenylborinic acid was prepared using method A and was treated with 8-hydroxyquinoline (0.5M solution in ethanol). A yellow precipitate formed immediately and was collected by filtration and washed with ethanol. The product had the following properties upon analysis: mp 192-194 °C; ^{1}H-NMR (360 MHz, C^2HCl_3,): δ 8.49 (dd, J = 4.6, 1.0 Hz, 1H), 8.43 (dd, J = 8.2, 1.0 Hz, 1H), 7.70 (dd,

J = 8.5, 7.7Hz, 1H), 7.66 (dd, J = 8.2, 4.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 4H), 7.26 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.2 Hz, 4H), 7.17 (d, J = 7.7 Hz, 1H); MS (+ve APCI) m/z 377 ($[M+H]^+$, ^{10}B, ^{35}Cl, ^{35}Cl), 378 ($[M+H]^+$, ^{11}B, ^{35}Cl, ^{35}Cl), 379 ($[M+H]^+$, ^{10}B, ^{35}Cl, ^{37}Cl), 380 ($[M+H]^+$, ^{11}B, ^{35}Cl, ^{37}Cl), 381 ($[M+H]^+$, ^{10}B, ^{37}Cl, ^{37}Cl), 382 ($[M+H]^+$, ^{11}B, ^{37}Cl, ^{37}Cl); Anal. ($C_{21}H_{14}NOBCl_2$) C, H, N.

Di-(3-chlorophenyl)borinic acid 8-hydroxyquinoline ester (11iv): Di-(3-chlorophenyl)borinic acid was formed using method A and was treated with 8-hydroxyquinoline (1.0 M in ethanol). The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel using CH_2Cl_2/hexane (1:1) to elute the product. The solvent was evaporated and the product crystallized upon the addition of ethanol. The solid was collected by filtration and washed with cold ethanol to yield the title product as a yellow solid having the following properties: mp 144 – 145°C ; ^{1}H-NMR (360 MHz, $C^2H_3O^2H$): 8.83 (d, J = 5.0 Hz, 1H), 8.63 (d, J = 8.2 Hz, 1H), 7.78 (dd, J = 8.6, 5.0 Hz, 1H), 7.67 (t, J = 8.2, 1H), 7.36 (d, J = 8.2, 1H), 7.26-7.09 (m, 9H); MS (+ve ESI) 377 ($[M+H]^+$, ^{10}B, ^{35}Cl, ^{35}Cl), 378 ($[M+H]^+$, ^{11}B, ^{35}Cl, ^{35}Cl), 379 ($[M+H]^+$, ^{10}B, ^{35}Cl, ^{37}Cl), 380 ($[M+H]^+$, ^{11}B, ^{35}Cl, ^{37}Cl), 381 ($[M+H]^+$, ^{10}B, ^{37}Cl, ^{37}Cl), 382 ($[M+H]^+$, ^{11}B, ^{37}Cl, ^{37}Cl); Anal. ($C_{21}H_{14}NOBCl_2$) C, H, N.

Di-(4-chloro-2-fluorophenyl)borinic acid 8-hydroxyquinoline ester (11v): Di-(4-chloro-2-fluorophenyl)borinic acid was formed using method A and was treated with 8-hydroxyquinoline (0.5M in ethanol). The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (3:1). The solvent was evaporated and the product crystallized upon the addition of ethanol. The solid was collected by filtration and washed with cold ethanol to yield the title product as a yellow solid having the following properties: mp 135°C; ^{1}H-NMR (360 MHz, $C^2H_3O^2H$): 8.82 (d, J = 5.0 Hz, 1H), 8.61 (d, J = 8.2 Hz, 1H), 7.75 (dd, J = 8.2, 5.0 Hz, 1H), 7.63 (t, J = 8.2 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.27 (t, J = 7.7 Hz, 2H), 7.13-6.90 (m, 5H); MS (+ve APCI) 413 ($[M+H]^+$, ^{10}B, ^{35}Cl, ^{35}Cl), 414 ($[M+H]^+$, ^{11}B, ^{35}Cl, ^{35}Cl), 415 ($[M+H]^+$, ^{10}B, ^{35}Cl, ^{37}Cl), 416 ($[M+H]^+$, ^{11}B, ^{35}Cl, ^{37}Cl), 417 ($[M+H]^+$, ^{10}B, ^{37}Cl, ^{37}Cl), 418 ($[M+H]^+$, ^{11}B, ^{37}Cl, ^{37}Cl); Anal. calcd for $C_{21}H_{12}NOBF_2Cl_2(0.5\ H_2O)$: C 59.62, H 3.10, N 3.31; found: C 59:74, H 3.03, N 3.18.

Di-(3,4-methylenedioxyphenyl)borinic acid 8-hydroxyquinoline ester (11vi): Di(3,4-methylenedioxyphenyl)borinic acid was formed using method A and was treated with 8-hydroxyquinoline (0.5M in ethanol). The solution was allowed to stand overnight to crystallize. The solid was collected by filtration and washed with cold ethanol to yield the product as a yellow solid having the following properties: mp 174-176 °C; ^{1}H-NMR (400 MHz, C^2HCl_3): 8.52 (d, J = 4.9 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.63 (dd, J = 8.2, 5.0 Hz, 1H), 7.25 (d, 1H), 7.17 (d, J = 7.7 Hz, 1H), 6.91 (s, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.2 Hz, 2H), 5.87 (s, 4H); MS (+ve APCI) m/z 397 (M^+, ^{10}B), 398 (M^+, ^{11}B); Anal. ($C_{23}H_{16}BNO_5$) C, H, N.

Di-(4-methoxyphenyl)borinic acid 8-hydroxyquinoline ester (11vii): Di(4-methoxyphenyl) borinic acid was formed using method A and was treated with 8-hydroxyquinoline (0.5M in ethanol) causing the title product to precipitate from the solution. The solid was collected by filtration and washed with cold ethanol to yield the product as a yellow solid having the following properties: mp 222-224°C; ^{1}H-NMR (400 MHz, C^2HCl_3): 8.53 (d, J = 5.0 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.61 (dd, J = 8.3, 5.0 Hz, 1H), 7.38 (d, J = 8.5 Hz, 4H), 7.24 (d, J = 8.2 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 8.6 Hz, 4H), 3.78 (s, 6H); MS (+ve MALDI, CHCA) m/z 369 ($[M+H]^+$, ^{10}B), 370 ($[M+H]^+$, ^{11}B); Anal. ($C_{23}H_{20}BNO_3$) C, H, N.

Di-(2-thienyl)borinic acid 8-hydroxyquinoline ester (11viii): Di-(2-thienyl)phenylborinic acid was prepared using method 2 and was treated with 8-hydroxyquinoline (0.5M solution in ethanol). A yellow precipitate formed upon standing and was collected by filtration and washed with ethanol. The isolated product had the following properties: mp 151-152 °C; ^{1}H-NMR (360 MHz, C^2HCl_3): δ 8.58 (d, 1H, J = 5.4 Hz), 8.39 (d, J = 8.7 Hz, 1H), 7.62 (t, J = 8.2, 1H), 7.60 (dd, J = 8.7, 5.4 Hz, 1H), 7.39 (dd, J = 4.6, 1.0 Hz, 4H), 7.26 (d, J = 8.2 Hz, 1H), 7.22 (dd, J = 3.4, 1.0 Hz, 2H), 7.20 (d, J = 8.2 Hz, 1H), 7.08 (dd, J = 4.6, 3.4 Hz, 2H); MS (+ve APCI) m/z 321 ($[M+H]^+$, ^{10}B), 322 ($[M+H]^+$, ^{11}B); Anal. Calc for $C_{17}H_{12}$ $BONS_2$ 0.7(H_2O): C 61.17, H 4.05, N 4.20; found C 61.15, H 4.09, N 4.25.

Di-(p-fluorophenyl)borinic acid 8-hydroxyquinaldine ester (12ii): Di-(p-fluorophenyl) borinic acid was formed using method A and was treated with 8-hydroxyquinaldine (0.5M solution in ethanol). The product was collected by filtration and washed with ethanol. The purified product had the following properties: mp 154-156 °C; ^{1}H-NMR (360 MHz, C^2HCl_3): 8.21 (d, J = 8.7 Hz, 1H) 7.47 (t, J = 8.2 Hz, 1H), 7.28 (d, J= 8.4, 1H), 7.22 (m, 4H), 7.12 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.85 (m, 4H) 2.39 (s, 3H); MS (+ve, APCI) m/z 359 ($[M+H]^+$, ^{10}B), 360 ($[M+H]^+$, ^{11}B); Anal. ($C_{22}H_{16}NBOF_2$) C, H, N.

Di-(p-chlorophenyl)borinic acid 8-hydroxyquinaldine ester (12iii): Di-(p-chlorophenyl)-borinic acid was formed using method A and was treated with chloroquinaldine (0.5M solution in ethanol). The product was collected by filtration and washed with ethanol. The purified product had the following properties: mp 155-156 °C; ^{1}H-NMR (360 MHz, C^2HCl_3): 8.21 (d, J = 8.6 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.27 (d, J = 8.2 Hz, 1H), 7.18 – 7.11 (m, 9H), 6.97 (d, J = 7.8 Hz, 1H) 2.38 (s, 3H); MS (+ve, APCI) m/z 392 (M^+, ^{11}B, ^{35}Cl, ^{35}Cl), 394 (M^+, ^{11}B, ^{35}Cl, ^{37}Cl), 396 (M^+, ^{11}B, ^{37}Cl, ^{37}Cl); Anal. ($C_{22}H_{16}NBOCl_2$) C, H, N.

Di-(4-methoxyphenyl)borinic acid 8-hydroxyquinaldine ester (12vii): Di-(4-methoxyphenyl) borinic acid was formed using method A and was treated with 8-hydroxyquinaldine (0.5M in ethanol). The solution was allowed to stand overnight to crystallize. The solid was collected by filtration and washed with cold ethanol to yield the title product as a yellow solid having the following properties: mp 150-151 °C; ^{1}H-NMR (400 MHz, C^2HCl_3): 8.29 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 8.5, 4H), 7.20 (d, J = 8.2 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 6.84 (d, J = 8.5 Hz, 4H), 3.79 (s, 6H), 2.54 (s, 3H); MS (+ve MALDI, CHCA) m/z 383 ($[M+H]^+$, ^{10}B), 384 ($[M+H]^+$, ^{11}B); Anal. ($C_{24}H_{22}BNO_3$) C, H, N.

Di-(p-fluorophenyl)borinic acid 5-chloro-8-hydroxyquinaline ester (13ii): Di-(p-fluorophenyl) borinic acid was formed using method A and was treated with 5-chloro-8-hydroxy quinaline (0.5M solution in ethanol). The product was collected by filtration and washed with ethanol. The purified product had the following

properties: mp 143-145 °C; ^{1}H-NMR (360 MHz, C^2HCl_3): 8.55 (d, J = 8.3 Hz, 1H), 8.45 (d, J = 5.0 Hz, 1H), 7.63 (m, 1H), 7.58 (d, J = 8.15 Hz, 1H), 7.22 (m, 4H), 6.98 (d, J = 8.14 Hz, 1H), 6.84 (m, 4H); MS (+ve, APCI) m/z 380 ($[M+H]^+$, ^{11}B); Anal. ($C_{21}H_{13}NBOClF_2$) C, H, N.

Di-(p-chlorophenyl)borinic acid 5-chloro-8-hydroxyquinaline ester (13iii): Di-(p-chlorophenyl)borinic acid was formed using method A and was treated with 5-chloro-8-hydroxy quinaline (0.5M solution in ethanol). The product was collected by filtration and washed with ethanol. The purified product had the following properties: mp = 154-156°C; ^{1}H-NMR (360 MHz, C^2HCl_3): 8.56 (d, J = Hz, 1H), 8.44 (d, J = Hz, 1H), 7.64 (m, 1H), 7.57 (d, J = Hz, 1H), 7.14 (m, 9 H), 6.98 (d, 1H); MS (+ve, ESI) m/z 412 ($[M+H]^+$, ^{10}B, ^{35}Cl, ^{35}Cl, ^{35}Cl), 413 ($[M+H]^+$, ^{11}B, ^{35}Cl, ^{35}Cl, ^{35}Cl); Anal. ($C_{21}H_{13}NBOCl_2$) C, H, N.

Di-(3,4-methylenedioxyphenyl)borinic acid 5-chloro-8-hydroxyquinoline ester (13vi): Di-(3,4-methylenedioxyphenyl)borinic acid was formed using method A and was treated with hot 5-chloro-8-hydroxyquinoline (0.5M in ethanol). The solution was allowed to stand overnight to crystallize. The solid was collected by filtration and washed with cold ethanol to yield the product as a yellow solid having the following properties: mp 212-213°C; ^{1}H-NMR (360 MHz, C^2HCl_3): 8.66 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 4.9 Hz, 1H), 7.75 (dd, J = 8.5, 5.1 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.88 (s and d, overlapping, 4H), 6.76 (d, J = 7.6 Hz, 2H), 5.88 (s, 4H); MS (+ve, APCI) m/z 432 ($[M+H]^+$, ^{11}B, ^{35}Cl), 434 ($[M+H]^+$, ^{11}B, ^{37}Cl); Anal. ($C_{23}H_{15}BClNO_5$) C, H, N.

Di-(4-methoxyphenyl)borinic acid 5-chloro-8-hydroxyquinoline ester (13vii): Di-(4-methoxyphenyl)borinic acid was formed using method A and was treated with hot 5-chloro-8-hydroxyquinoline (0.5m in ethanol). The solution was allowed to stand overnight to crystallize. The solid was collected by filtration and washed with cold ethanol to yield the title product as a yellow solid having the following properties: mp 184-185°C; ^{1}H-NMR (400 MHz, C^2HCl_3): 8.66 (d, J = 8.3 Hz, 1H), 8.59 (d, J = 5.1 Hz, 1H), 7.73 (dd, J = 8.4, 5.1 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 8.6 Hz, 4H), 7.09 (d, J = 8.3 Hz, 1H), 6.84 (s, J = 8.6 Hz, 4H),

3.78 (s, 6H); MS (+ve APCI) m/z 403 (M^+, ^{11}B, ^{35}Cl), 405 (M^+, ^{11}B, ^{37}Cl); Anal. ($C_{23}H_{19}BClNO_3$) C, H, N.

Di-(3,4-methylenedioxyphenyl)borinic acid 8-hydroxy-5-nitroquinoline ester (14vi):

Di-(3,4-methylenedioxyphenyl)borinic acid was formed using method A and was treated with hot 8-hydroxy-5-nitroquinoline (0.5m in ethanol). The solution was allowed to stand overnight to crystallize. The solid was collected by filtration and washed with cold ethanol to yield the product as a yellow solid having the following properties: mp 243-245°C; ^{1}H-NMR (360 MHz, C^2HCl_3): 9.69 (d, J = 8.7 Hz, 1H), 8.90 (d, J = 8.8 Hz, 1H), 8.68 (d, J = 5.0 Hz, 1H), 7.97 (dd, J = 8.7, 5.0 Hz, 1H), 7.17 (d, J = 8.9 Hz, 1H), 6.84 (s, 2H), 6.82 (d, J = 7.8 Hz, 2H), 6.77 (d, J = 7.7 Hz, 2H), 5.90 (s, 4H); MS (+ve APCI) 442 (M^+, ^{11}B); Anal. ($C_{23}H_{15}BN_2O_7$) C, H, N.

Diphenylborinic acid 2-aminophenol (15i): Diphenylborinic acid was prepared using method B and was treated with 2-aminophenol (1M solution in ethanol). A white precipitate formed upon standing and was collected by filtration and washed with ethanol. The purified product had the following properties: mp 179-181°C; ^{1}H-NMR (360 MHz, $C^2H_3O^2H$): δ 7.44 (m, 4H), 7.18 (m, 6H), 6.90 (dd, 1H), 6.76 (dd, 1H), 6.62 (m, 2H); MS (+ve,APCI) m/z 274 ($[M+H]^+$, ^{11}B); Anal. ($C_{18}H_{16}NOB$): C, H, N.

Diphenylborinic acid pyridine-2-methanol (16i): Diphenylborinic acid was prepared using method B and was treated with pyridine-2-methanol (1M solution in ethanol). A white precipitate formed upon standing and was collected by filtration and washed with ethanol; mp 152-153°C; ^{1}H-NMR (360 MHz, C^2HCl_3): δ 8.40 (d, J = 6.0 Hz, 1H), 7.98 (t, J = 7.7 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.30 (m, 4H), 7.23 (m, 7H); MS (+ve, APCI) m/z 274 ($[M+H]^+$, ^{11}B); Anal. ($C_{18}H_{16}NOB$): C, H, N.

Diphenylborinic acid 2-amino-1-phenylpropanol (17i): Diphenylborinic acid was prepared using method B and was treated with 2-amino-1-phenylpropanol (1M solution in ethanol). A white precipitate formed upon standing and was collected

by filtration and washed with ethanol. The purified product had the following properties: mp 200-201°C; ^{1}H-NMR (360 MHz, $C^2H_3O^2H$): δ 7.70-7.10 (m, 15H), 5.03 (dd, J = 9.2, 6.4 Hz, 1H), 3.32 (dd, J = 10.9, 6.4 Hz, 1H), 2.81 (dd, J = 10.9, 9.2 Hz, 1H); MS (+ve, APCI) m/z 302 ([M+H]$^+$, ^{11}B); Anal. ($C_{20}H_{20}NOB$) C, H, N.

Diphenylborinic acid (S)-(+)-pyrrolidine-2-methanol (18i): Diphenylborinic acid was prepared using method B and was treated with (S)-(+)-pyrrolidine-2-methanol (1M solution in ethanol). A white precipitate formed upon standing and was collected by filtration and washed with ethanol. The purified product had the following properties: mp 221-222°C; ^{1}H-NMR (360 MHz, $C^2H_3O^2H$): δ 7.44 (m, 4H), 7.13 (m, 6H), 3.94 (dd, J = 6.6, 8.7 Hz, 1H), 3.77 (m, 1H), 3.68 (dd, J = 6.6, 8.7 Hz, 1H), 2.86 (m, 1H), 2.60 (m, 1H), 2.14 (m, 1H), 1.93-1.65 (m, 3H); MS (+ve, APCI) m/z 266 ([M+H]$^+$, ^{11}B); Anal. ($C_{17}H_{20}NOB$) C, H, N.

Di-(4-fluorophenyl)borinic acid ethanolamine ester (19ii): Di-(4-fluorophenyl)borinic acid was prepared using method A and was treated with ethanolamine (1M solution in ethanol). A white precipitate formed upon standing and was collected by filtration and washed with ethanol. The purified product had the following properties: mp 247-249°C; ^{1}H-NMR (360 MHz, $C^2H_3O^2H$): δ 7.37 (dd, J = 8.7, 6.4 Hz, 4H), 6.90 (t, J = 8.7 Hz, 4H), 3.95 (d, J = 6.4 Hz, 2H), 3.02 (d, J = 6.4 Hz, 2H); MS (+ve APCI) m/z 261 ([M+H]$^+$, ^{10}B), 262 ([M+H]$^+$, ^{11}B); Anal. ($C_{14}H_{14}NOBF_2$) C, H, N.

Di-(4-chlorophenyl)borinic acid ethanolamine ester (19iii): Di-(4-chlorophenylborinic acid was prepared using method A and was treated with ethanolamine (1M solution in ethanol). A white precipitate formed upon standing and was collected by filtration and washed with ethanol. The purified product had the following properties: mp 241-242°C; ^{1}H-NMR (360MHz, $C^2H_3O^2H$): δ 7.35 (d, J = 8.6, 4H), 7.18 (d, J = 8.6, 4H), 3.94 (d, J = 6.4 Hz, 2H), 3.02 (d, J = 6.4 Hz, 2H); MS (+ve APCI) m/z 293 ([M+H]$^+$, ^{10}B, ^{35}Cl, ^{35}Cl), 294 ([M+H]$^+$, ^{11}B, ^{35}Cl, ^{35}Cl), 295 ([M+H]$^+$, ^{10}B, ^{35}Cl, ^{37}Cl), 296 ([M+H]$^+$, ^{11}B, ^{35}Cl, ^{37}Cl), 297 ([M+H]$^+$, ^{10}B, ^{37}Cl, ^{37}Cl), 298 ([M+H]$^+$, ^{11}B, ^{37}Cl, ^{37}Cl); Anal. ($C_{14}H_{14}NOBCl_2$) C, H, N.

EXAMPLE 2

Biological Activity Assays

The antibacterial activity of the compounds prepared as descried above were tested using *Caulobacter crescentus* and *Bacillus subtilis* as follows.

***Caulobacter crescentus* cell growth assay**

Caulobacter crescentus (CB15N) was grown in PYE media (Sambrook *et al.*, 1989, Molecular Cloning: A Laboratory Manual, 2d ed., Cold Spring Harbor Press: N.Y.) overnight at 30°C to saturation. Taking advantage of the inherent ampicillin resistance of *Caulobacter crescentus* to minimize the risk of contamination, this saturated culture was diluted in PYE media containing 200 μg/mL ampicillin to a final OD_{600} of 0.05. Aliquots (146 μL) of this diluted cell culture were placed in wells of a microtiter plate. An inhibitor (4 μL of a stock solution of an appropriate concentration dissolved in either dimethylformamide or dimethylsulfoxide) was added to each of these wells to give a final volume of 150 μL. This plate was incubated at 30°C with gentle shaking at 550 rpm in an Eppendorf Thermomixer R. Control experiments were performed in parallel. These consisted of wells containing: i) 150 μL PYE/ampicillin media (no cell culture) as a blank; and ii) 146 μL diluted cell culture and 4 μL (DMF or DMSO) for maximum cell growth in the presence of solvent and absence of inhibitor. Cell growth was monitored at 630 nm using a microtitre plate reader at time points of: 0 hours, 4 hours, 8 hours, and 22 hours. The final cell growth was recorded as a percent of the maximum cell growth.

***Bacillus subtilis* cell growth assay**

A similar cell growth assay to that described for *Caulobacter crescentus* was performed with *Bacillus subtilis* (ATCC #33234). The following changes were incorporated to accommodate the different growth conditions: i) cells were grown in Luria-Bertani (LB) media without antibiotics (Sambrook *et al.*, *ibid.*); ii) growth temperature was 37°C; and iii) cell growth was monitored at time points of 0 hours, 2.5 hours, 5 hours, and 7.5 hours. After 7.5 hours any culture with

inhibited cell growth was diluted 500-fold into fresh LB media. Recovery from inhibitor selection was assessed after 12 hours at 37°C.

CcrM inhibition assay

Methyltransferase activity was measured by monitoring the incorporation of [^{3}H]CH_3 from [^{3}H]-*S*-adenosylmethionine (SAM) into DNA. A stock solution containing 250 nM CcrM, 5 μM N645/50 mer (the sequence of which is identified below), 150 mM potassium acetate, 5 mM 2-mercaptoethanol in pH 7.5 HEPES buffer was prepared. Aliquots were placed in Eppendorf tubes and inhibitors were added from concentrated stock solutions (16.7 mM in DMF or DMSO) to reach the appropriate final concentrations (500 μM or 100 μM) in a total of 15 μL. Reactions were initiated by the addition of [^{3}H]SAM at a final concentration of 50 μM. After 40 mins at 30°C, 5 μL aliquots were removed from the reaction and spotted onto DE81 anion exchange filter circles. The filters were allowed to dry and then washed with 3 x 200 mL of 0.3 M ammonium formate to remove unreacted [^{3}H]SAM, followed by 2 x 200 mL 95 % ethanol wash and finally a 200 mL ether wash. The filters were allowed to air dry and counted by standard liquid scintillation techniques. Control reactions in the absence of inhibitors were used to determine the extent of inhibition. High throughput screening was carried out similarly in Tris-HCl buffer (50 μM, pH 7.5) with plasmid DNA as substrate (Litmus 29 (New England Biolabs): 250 μM DNA, 3 μM sites), 100 μM inhibitor candidate and enzyme, potassium acetate and 2-mercaptoethanol concentrations as described above. Assays were initiated with [$^{14}CH_3$]SAM (50 μM, 34 Ci/mol) in a volume of 10 μL in a PCR plate, and incubated for 30 minutes at 30°C. Four microliter aliquots were then spotted on DE81 paper with a multichannel pipette and washed and dried as described above. Data was collected with a Molecular Dynamics model 425S phosphorimager, and analyzed with the spotfinder utility in ImageQuant 3.3.

DNA substrate [N645/50 mer]

CH_3
5'-ATC CTC TCG C**GA ATC** AAC AGA AAT ATC CGC TCA TCA CCG CAA GTT
3'- AG GAG AGC G**CT TAG** TTG TCT TTA TAG GCG AGT AGT GGC GTT CAA AAG GCA A

(where the methylated strand shown above is SEQ ID No. 1 and the complementary strand is SEQ ID No. 2). Synthesis of DNA was achieved on an Expedite BioSystems DNA synthesizer and purified as previously described (Capson *et al.*, 1992, *Biochemistry* 31: 10984-10994).

Table I

Compound	% reaction *Brucella abortus* CcrM Activity	IC_{50} (μM) *Caulobacter crescentus* Cell Growth	IC_{50} (μM) *Bacillus subtilis* Cell Growth
(11i)		>100	nt
(11ii)	61	23	nt
(11iii)	61	16	nt
(11iv)		10	<10
(11v)		26	<10
(11vi)	42	32	28
(11vii)		24	20
(11viii)	74	>100	28
(12ii)	17	56	>100
(12iii)	40	5	24
(12vii)	56	24	>100
(13ii)	55	7	27
(13iii)	81	6	<10
(13vi)		7	>100
(13vii)		7	36
(14vi)	21	7	>100
(15i)	38	>100	>100
(16i)	93	>100	>100
(17i)	114	>100	>100
(18i)	81	>100	>100
(19ii)	8	85	nt
(19iii)		17	nt

These results indicate that the compounds of the invention have useful IC50 values for inhibiting CcrM and DAM methylases in bacteria.

These compounds have advantageous physical properties, and are isolated as pure, stable solids that are amenable to large-scale production. Additional specific embodiments of adenine DNA methyltransferase inhibitors of the invention includes related compounds having these additional features:

1) Analogues with various substituents on the phenyl rings in any, or combination of, the ortho-, meta- and para- positions, including fused rings and substituted fused rings;

2) Analogues having aromatic heterocycles of various ring sizes, substituted heterocycles, fused heterocycles and substituted fused heterocycles in place of one or both phenyl groups;

3) Analogues having two non-identical aromatic rings bound to the boron atom, using combinations of the aromatic systems described in 1) and 2) above;

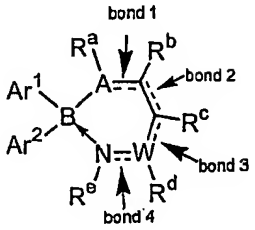
4) Analogues prepared using quinolines **(9)** containing various substituents in any possible position or structural analogues including fused heteroaromatic rings containing one or more heteroatom in any possible position or fused heteroaromatic rings containing one or more heteroatom in any possible position and containing various substituents in any possible position; and

5) Analogues having substitutions on either, or both of, the C-1 and C-2 positions of the ethylene group of the 2-aminoethanol of **(10)**.

It should be understood that the foregoing disclosure emphasizes certain specific embodiments of the invention and that all modifications or alternatives equivalent thereto are within the spirit and scope of the invention as set forth in the appended claims.

WHAT WE CLAIM IS:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof,

wherein A is N, O or S;

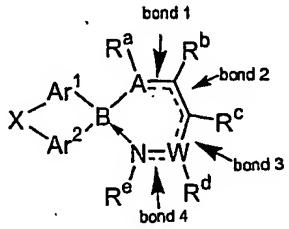
W is C_p, where p is 0 or 1;

R^a, R^b, R^c, R^d, and R^e are the same or different and are independently hydrogen, halogen, nitro, nitroso, lower alkyl, aryl or substituted aryl, lower alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl or cycloalkyl group is optionally substituted with halogen, lower alkyl or lower alkoxy, aryl or substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, ester, or sulfate, or wherein R^a, R^b, R^c, R^d, and R^e may be connected by aromatic, aliphatic, heteroaromatic, heteroaliphatic ring structures or substituted embodiments thereof, where R^a is absent when A is O or S and R^d is absent when p = 0; and

wherein Ar^1 and Ar^2 can be the same or different and are each independently aryl or aryl substituted at one or a plurality of positions with halogen, nitro, nitroso, lower alkyl, aryl or substituted aryl, lower alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl or cycloalkyl group is optionally substituted with

halogen, lower alkyl or lower alkoxy, aryl or substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, ester, or sulfate, and

optionally Ar1 and Ar2 maybe cojoined to create a tricyclic scaffold, where X = C=O, CHOH, $(CH_2)_n$ (n = 0 to 2), -CH=CH-, NR^f (R^f = H, C_1-C_4 alkyl, phenyl, thienyl, or pyridyl), O, SO_n (n = 0 to 2), which have a plurality of positions with halogen, nitro, nitroso, lower alkyl, aryl or substituted aryl, lower alkoxy, lower alkoxyalkyl, or cycloalkyl or cycloalkyl alkoxy, where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and



wherein bond 1, bond 2, bond 3 and bond 4 are independently a single bond or a double bond, provided that when A is S or O, bind 1 is a single bond and where A is N, bond 1 is a double bond.

2. A compound according to claim 1, selected from di-(4-fluorophenyl)borinic acid 8-hydroxyquinoline ester, di-(4-chlorophenyl)borinic acid 8-hydroxyquinoline ester, di-(3-chlorophenyl)borinic acid 8-hydroxyquinoline ester, di-(4-chloro-2-fluorophenyl)borinic acid 8-hydroxyquinoline ester, di-(3,4-methylenedioxyphenyl)borinic acid 8-hydroxyquinoline ester, di-(4-methoxyphenyl)borinic acid 8-hydroxyquinoline ester, di-(2-thienyl)borinic acid 8-hydroxyquinoline ester, di-(p-fluorophenyl)borinic acid 8-hydroxyquinaldine ester, di-(p-chlorophenyl)borinic acid 8-hydroxyquinaldine ester, di-(4-methoxyphenyl)borinic acid 8-hydroxyquinaldine ester, di-(p-fluorophenyl)borinic acid 5-chloro-8-hydroxyquinaline ester, di-(p-chlorophenyl)borinic acid 5-chloro-8-hydroxyquinaline ester, di-(3,4-methylenedioxyphenyl) borinic acid 5-chloro-8-hydroxyquinoline ester, di-(4-methoxyphenyl)borinic acid 5-chloro-8-hydroxyquinoline ester, di-(3,4-methylenedioxyphenyl)borinic acid 8-hydroxy-5-

nitroquinoline ester, diphenylborinic acid 2-aminophenol, diphenylborinic acid pyridine-2-methanol, diphenylborinic acid 2-amino-1-phenylpropanol, diphenylborinic acid (S)-(+)-pyrrolidine-2-methanol, di-(4-fluorophenyl)borinic acid ethanolamine ester, and di-(4-chlorophenyl)borinic acid ethanolamine ester.

3. A pharmaceutical composition comprising a compound according to Claim 1 combined with at least one pharmaceutically acceptable carrier or excipient.

4. A method for the treatment of a disease or disorder associated with infection with a pathogenic bacteria that expresses an adenine DNA methyltransferase, said method comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound of Claim 1.

5. A method according to Claim 4 wherein the disease or disorder associated infection with a pathogenic bacteria is *Staphylococcus aureus*; *Staphylococcus saprophyticus*; *Streptococcus pyrogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Bacillus anthracis*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *Neisseria gonorrhoeae*; *Neisseria meningitidis*; *Pseudomonas aeruginosa*; *Legionella pneumophila*; *Escherichia coli*; *Yersinia pestis*; *Hemophilus influenzae*; *Helicobacter pylori*; *Campylobacter fetus*; *Vibrio cholerae*; *Vibrio parahemolyticus*; *Trepomena pallidum*; *Actinomyces israelii*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus* or *Agrobacterium tumefaciens*.

6. A method for the treatment of a disease or disorder associated with infection with a pathogenic bacteria that expresses an adenine DNA methyltransferase, said method comprising administering to a patient in need of such treatment a therapeutically-effective amount of the pharmaceutical composition of Claim 3.

7. A method according to Claim 6 wherein the disease or disorder associated infection with a pathogenic bacteria is *Staphylococcus aureus*;

Staphylococcus saprophyticus; *Streptococcus pyrogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Bacillus anthracis*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *Neisseria gonorrhoeae*; *Neisseria meningitidis*; *Pseudomonas aeruginosa*; *Legionella pneumophila*; *Escherichia coli*; *Yersinia pestis*; *Hemophilus influenzae*; *Helicobacter pylori*; *Campylobacter fetus*; *Vibrio cholerae*; *Vibrio parahemolyticus*; *Trepomena pallidum*; *Actinomyces israelii*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus* or *Agrobacterium tumefaciens*.

8. A combinatorial library comprising a multiplicity of compounds according to claim 1.

9. A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 3 in a container and instructions for using the composition to treat a patient suffering from a disease or disorder associated with infection with a pathogenic bacterium.

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(54) Title: ANTIBIOTICS CONTAINING BORINIC ACID COMPLEXES AND METHODS OF USE

(57) Abstract: The structure and preparation of antibiotics incorporating borinic acid complexes are disclosed, especially hydroxyquinoline, imidazole and picolinic acid derivatives, along with compositions of these antibiotics and methods of using the antibiotics and compositions as bactericidal and fungicidal agents as well as therapeutic agents for the treatment of diseases caused by bacteria and fungi.

ANTIBIOTICS CONTAINING BORINIC ACID COMPLEXES AND METHODS OF USE

This application claims priority of U.S. Provisional Application Serial No. 60/434,375, filed 18 December 2002, Serial No. 60/436,095, filed 23 December 2002, and Serial No. 60/437,849, filed 3 January 2003, the disclosures of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to the field of antibiotics and particularly antibacterial and antifungal compounds and uses thereof. Methods for preparing and using these antibiotics, and pharmaceutical compositions thereof, are also provided.

BACKGROUND OF THE INVENTION

One hallmark of the modern era of medicine has been the decline in morbidity and mortality associated with bacterial and fungal infections. However, misuse of conventional antibiotics and natural selection of the infectious bacterial population has resulted in the development of varying degrees of drug resistance by most bacterial infectious agents to most antibiotic agents. In severe cases, such as MRSA (Multidrug-Resistant StaphA), one or only a few antibiotics are currently effective. In addition, the

existence of immunodeficiency syndromes results in additional incidence of opportunistic infections requiring intensive antibiotic treatment.

Thus, there continues to be a need in the medical arts for novel, more effective, antibiotic compounds, especially for treating bacterial infections, that are resistant to currently available therapies.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention relates to antibiotic compounds. The antibiotic compounds of the invention are borinate derivatives, especially borinic acid complexes, and include such compounds as derivatives of hydroxyquinolines, picolinic acids and imidazoles.

The antibiotic compounds are also provided as pharmaceutical compositions that can be administered to an animal, most preferably a human, for treatment of a disease having a bacterial or fungal etiology, or an opportunistic infection with a bacteria or fungus in an animal, most preferably a human, in an immunologically compromised or debilitated state of health.

In preferred embodiments, the compounds of the invention are those having the structures given by Formulas 1 or 2, with preferred substituents as disclosed herein.

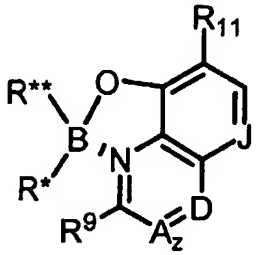
The invention also provides methods for preparing the antibiotic compounds and pharmaceutical compositions thereof, and methods of using said antibiotics therapeutically. Kits and packaged embodiments of the antibiotic compounds and pharmaceutical compositions of the invention are also contemplated.

The invention also relates to methods of treating infections, preferably bacterial and/or fungal infections, using the antibiotic compounds disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

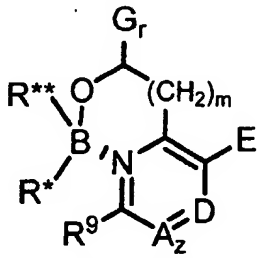
This invention provides antibiotics, and specifically antibacterial and anti-fungal compounds, useful in treating and/or preventing bacterial infections.

The invention comprises a compound having the structure with formula



Formula 1

or



Formula 2

wherein B is boron, O is oxygen, m is 0, 1, or 2,

wherein R* and R** are each independently selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 - C_6), substituted or unsubstituted vinyl, substituted or unsubstituted alkynyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, and substituted or unsubstituted heterocycle,

and wherein z is 0 or 1 and when z is 1, A is CH, CR^{10} or N,

and wherein D is N, CH, or CR^{12},

and wherein E is H, OH, alkoxy or N-(morpholinyl)ethoxy

and wherein r is 1 or 2, and wherein when r is 1, G is =O (double-bonded oxygen) and when r is 2, each G is independently H, methyl, ethyl or propyl,

wherein R^{12} is selected from $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2*-amino, 3*-amino, NH_2SO_2 and $CONH_2$,

and wherein J is CR^{10} or N

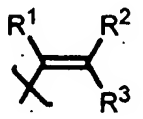
and wherein R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, $(CH_2)_nOH$ (n = 1 to 3), CH_2NH_2, $CH_2NHalkyl$, $CH_2N(alkyl)_2$, halogen, CHO, CH=NOH, CO_2H, CO_2-alkyl, S-alkyl, SO_2-alkyl, S-aryl, NH_2, alkoxy, CF_3, SCF_3, NO_2, SO_3H and OH,

including salts thereof, especially all pharmaceutically acceptable salts.

In a preferred embodiment of either of Formulas 1 or 2, one of R* and R** is a substituted or unsubstituted alkyl (C_1 - C_4) or R* and R** are each a substituted or unsubstituted alkyl (C_1 - C_4).

In a preferred embodiment of either of Formulas 1 or 2, one of R* and R** is a substituted or unsubstituted cycloalkyl (C_3 - C_6) or R* and R** are each a substituted or unsubstituted cycloalkyl (C_3 - C_6).

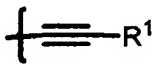
In a preferred embodiment of either of Formulas 1 or 2, one of R* and R** is a substituted or unsubstituted vinyl or R* and R** are each a substituted or unsubstituted vinyl. In a further preferred embodiment thereof, the vinyl has the structure



wherein R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl,

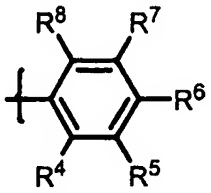
$(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

In a preferred embodiment of either of Formulas 1 or 2, one of R* and R** is a substituted or unsubstituted alkynyl or R* and R** are each a substituted or unsubstituted alkynyl. In a further preferred embodiment thereof the alkynyl has the structure



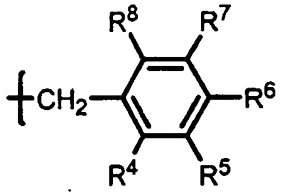
wherein R^1 is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

In a preferred embodiment of either of Formulas 1 or 2, one of R* and R** is a substituted or unsubstituted phenyl or R* and R** are each a substituted or unsubstituted phenyl. In a further preferred embodiment thereof the phenyl has the structure



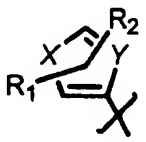
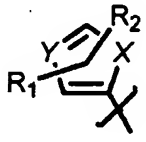
wherein R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2°-amino, 3°-amino, NH_2SO_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

In a preferred embodiment of either of Formulas 1 or 2, one of R* and R** is a substituted or unsubstituted benzyl or R* and R** are each a substituted or unsubstituted benzyl. In a further preferred embodiment thereof the benzyl has the structure



wherein R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2°-amino, 3°-amino, NH_2SO_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl..

In a preferred embodiment of either of Formulas 1 or 2, one of R* and R** is a substituted or unsubstituted heterocycle or R* and R** are each a substituted or unsubstituted heterocycle. In a further preferred embodiment thereof the heterocycle has the structure

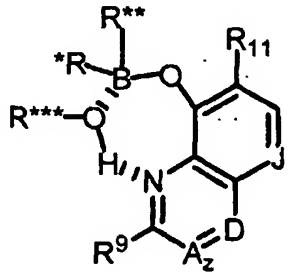

or


wherein X = CH=CH, N=CH, NR^{13} (wherein R^{13} = H, alkyl, aryl or benzyl), O, or S

and wherein Y = CH or N

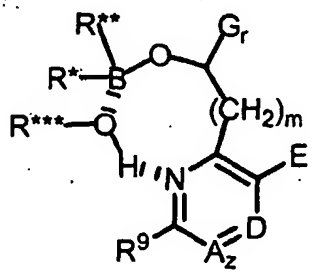
and wherein R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

The structures of the invention also permit solvent interactions that may afford structures (Formulas 1B and 2B) that include atoms derived from the solvent encountered by the compounds of the invention during synthetic procedures and therapeutic uses. Thus, such solvent structures can especially insinuate themselves into the compounds of the invention between the boron and nitrogen atoms, thereby affording a ring size one or two atom larger than that discloses in the structures herein. For example, where the boron ring of a structure of the invention comprises 5 atoms, including, for example, the boron, a nitrogen, an oxygen and 2 carbons, insinuation of a solvent atom between the boron and nitrogen would afford a 7 membered ring. In one example, use of hydroxyl and amino solvents may afford structures containing an oxygen or nitrogen between the ring boron and nitrogen atoms to increase the size of the ring. Such structures are expressly contemplated by the present invention where R*** is H or alkyl



Formula 1B (solvent adduct)

or



Formula 2B (solvent adduct)

As used herein, the following terms have the stated meaning:

By "alkyl", "lower alkyl", and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such

as, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkoxy", "lower alkoxy", and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

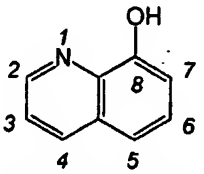
By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "cycloalkyl", e.g., C_3-C_7 cycloalkyl, in the present invention is meant cycloalkyl groups having 3-7 atoms such as, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. In the C_3-C_7 cycloalkyl groups, preferably in the C_5-C_7 cycloalkyl groups, one or two of the carbon atoms forming the ring can optionally be replaced with a hetero atom, such as sulfur, oxygen or nitrogen. Examples of such groups are piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, imidazolidinyl, oxazolidinyl, perhydroazepinyl, perhydrooxazapinyl, oxepanyl, and perhydrooxepanyl. C_3 and C_4 cycloalkyl groups having a member replaced by nitrogen or oxygen include aziridinyl, azetidinyl, oxetanyl, and oxiranyl.

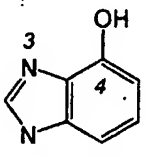
By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy. Preferred aryl groups include phenyl and naphthyl, each of which is optionally substituted as defined herein.

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, pyridyl, pyrimidinyl, (iso)quinolinyl, napthyridinyl, benzimidazolyl, and benzoxazolyl. Preferred heteroaryls are thiazolyl, pyrimidinyl, preferably pyrimidin-2-yl, and pyridyl. Other preferred heteroaryl groups include 1-imidazolyl, 2-thienyl, 1-, or 2-quinolinyl, 1-, or 2- isoquinolinyl, 1-, or 2-tetrahydroisoquinolinyl, 2- or 3- furanyl and 2- tetrahydro-furanyl.

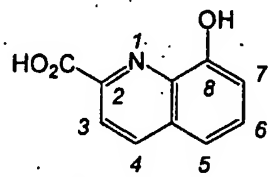
By "ligand" is meant a nitrogen-containing aromatic system which is capable of forming a dative bond with the Lewis acidic boron center, while appended as a borinate ester moiety. Such ligands are known to those trained in the arts. Examples are shown in the structures below.



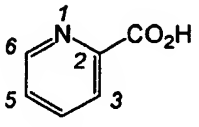
8-hydroxyquinoline



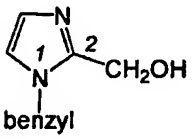
4-hydroxybenzimidazole



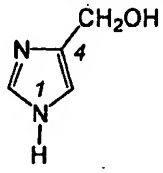
8-hydroxyquinoline-2-carboxylic acid



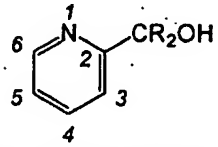
picolinic acid (pyridine-2-carboxylic acid)



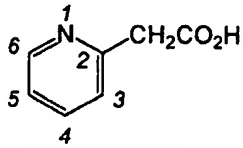
2-hydroxymethyl-1N-benzylimidazole



4-hydroxymethyl-imidazole



2-(hydroxymethyl)pyridine R = H
2-(hydroxyisopropyl)pyridine R = Me



2-pyridylacetic acid

The compounds of the present invention have been implicated in the inhibition of key microbial enzymes, such as bacterial DNA methyltransferase. Many of the compounds disclosed herein are selective inhibitors of methyltransferases in microbes, while not inhibitory for methyltransferases in mammals. However, the anti-bacterial and anti-fungal activity of the compounds of the invention is not limited to those with said enzyme inhibitory activity, nor is the latter effect necessarily essential to said therapeutic activity.

The invention also provides embodiments of the compounds disclosed herein as pharmaceutical compositions. The pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, *e.g.*, by means of a conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, hydroxyethanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and functional equivalents. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

For injection, the compounds of the invention can be formulated in appropriate aqueous solutions, such as physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal and transcutaneous administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane,

dichlorotetra-fluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin for use in an inhaler, can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use. The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations

can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system can be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system can be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components can be varied: for example, other low-toxicity nonpolar surfactants can be used instead of polysorbate 80; the fraction size of polyethylene glycol can be varied; other biocompatible polymers can replace polyethylene glycol, *e.g.* polyvinyl pyrrolidone; and other sugars or polysaccharides can substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethyl sulfoxide also can be employed, although usually at the cost of greater toxicity. Additionally, the compounds can be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by

those skilled in the art. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein and nucleic acid stabilization can be employed.

The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

The compounds of the invention can be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, phosphoric, hydrobromic, sulfinic, formic, toluenesulfonic, methanesulfonic, nitic, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Pharmaceutical compositions of the compounds of the present invention can be formulated and administered through a variety of means, including systemic, localized, or topical administration. Techniques for formulation and administration can be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA. The mode of administration can be selected to maximize delivery to a desired target site in the body. Suitable routes of administration can, for example, include oral, rectal, transmucosal,

transcutaneous, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one can administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a specific tissue, often in a depot or sustained release formulation.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays, as disclosed herein. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC_{50} (effective dose for 50% increase) as determined in cell culture, *i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of bacterial cell growth. Such information can be used to more accurately determine useful doses in humans.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug

combination, the severity of the particular disease undergoing therapy and the judgment of the prescribing physician.

For administration to non-human animals, the drug or a pharmaceutical composition containing the drug may also be added to the animal feed or drinking water. It will be convenient to formulate animal feed and drinking water products with a predetermined dose of the drug so that the animal takes in an appropriate quantity of the drug along with its diet. It will also be convenient to add a premix containing the drug to the feed or drinking water approximately immediately prior to consumption by the animal.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová *et al.* (1996, *J. Chromat. B* 677: 1-27). Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds that exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in

formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See, e.g.* Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch.1, p.1).

Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety that are sufficient to maintain bacterial cell growth inhibitory effects. Usual patient dosages for systemic administration range from 100 - 2000 mg/day. Stated in terms of patient body surface areas, usual dosages range from 50 - 910 mg/m^2/day. Usual average plasma levels should be maintained within 0.1-1000 μM. In cases of local administration or selective uptake, the effective local concentration of the compound cannot be related to plasma concentration.

The compounds of the invention are useful as antibiotics for the treatment of diseases of both animals and humans, including but not limited to actinomycosis, anthrax, bacterial dysentery, botulism, brucellosis, cellulitis, cholera, conjunctivitis, cystitis, diphtheria, bacterial endocarditis, epiglottitis, gastroenteritis, glanders, gonorrhea, Legionnaire's disease, leptospirosis, bacterial meningitis, plague, bacterial pneumonia, puerperal sepsis, rheumatic fever, Rocky Mountain spotted fever, scarlet fever, streptococcal pharyngitis, syphilis, tetanus, tuberculosis, tularemia, typhoid fever, typhus, and pertussis.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The compounds of the invention comprise a novel class of broad-spectrum antibiotics. Medically-important bacterial species that provide

appropriate targets for the antibacterial activity of the inhibitors of the invention include gram-positive bacteria, including cocci such as *Staphylococcus* species and *Streptococcus* species; acid-fast bacterium, including *Mycobacterium* species; bacilli, including *Bacillus* species, *Corynebacterium* species and *Clostridium* species; filamentous bacteria, including *Actinomyces* species and *Streptomyces* species; gram-negative bacteria, including cocci such as *Neisseria* species and *Acinetobacter* species; bacilli, such as *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species, and *Streptobacillus* species; spirochetal species, *Campylobacter* species, *Vibrio* species; and intracellular bacteria including *Rickettsiae* species and *Chlamydia* species.

Specific bacterial species that are targets for the antibiotics of the invention include *Staphylococcus aureus*; *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Enterococcus faecalis*; *Enterococcus faecium*; *Bacillus anthracis*; *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Acinetobacter baumannii*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *Neisseria gonorrhoeae*; *Neisseria meningitidis*; *Pseudomonas aeruginosa*; *Legionella pneumophila*; *Escherichia coli*; *Yersinia pestis*; *Haemophilus influenzae*; *Helicobacter pylori*; *Campylobacter fetus*; *Campylobacter jejuni*, *Vibrio cholerae*; *Vibrio parahemolyticus*; *Trepomena pallidum*; *Actinomyces israelii*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus*; *Agrobacterium tumefaciens*; and *Francisella tularensis*.

In carrying out the procedures of the present invention it is of course to be understood that reference to particular buffers, media, reagents, cells,

culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

The invention is described in more detail in the following non-limiting examples. It is to be understood that these methods and examples in no way limit the invention to the embodiments described herein and that other embodiments and uses will no doubt suggest themselves to those skilled in the art.

The compounds of this invention are evaluated for their antibacterial activity as per the guidelines and procedures prescribed by the National Committee for Clinical Laboratory Standards (NCCLS) (cf., NCCLS Document M7-A3, 1993 –Antimicrobial Susceptibility Testing).

Protocol for MIC Determination

A useful protocol for MIC determination is as follows:

1. Approximately 2.5 mg of the compounds to be tested was weighed into cryovials.

2. 5 mg/ml stock solutions were made by adding DMSO to the samples accordingly.

3. 256 µg/ml working solutions were made by using the 5 mg/ml stock solutions and adding sterile distilled water accordingly.

4. A Beckman 2000 Automated Workstation was programmed to load 96 well plates with broth and compounds as follows:

-100 µl of the appropriate broth was added to columns 1-11
-200 µl of the appropriate broth was added to column 12
-100 µl of compounds at the 256 µg/ml working solution were added to column 1 (one compound per row)
-Two-fold serial dilutions were done from column 1 to 10
-Column 11 served as the growth control

5. The 10 organism panel was plated from stock vials stored at -80°C and incubated for 24 hours at 34°C. The organisms were then sub-cultured and incubated for 24 hours at 34°C.

-The inoculums were first prepared in sterile distilled water with a target of 0.09-0.11 absorbance at 620 nm wavelength
-A 1/100 dilution was made into the appropriate broth
-100 µl of broth with organism was added to columns 1-11
-Column 12 served as the blank control

6. The completed 96 well plates were incubated for 24 hours at 34°C. The 96 well plates were then read using a Beckman Automated Plate Reader at 650 nm wavelength. The MIC was determined through calculations involving the growth control (column 11) and blank control (column 12).

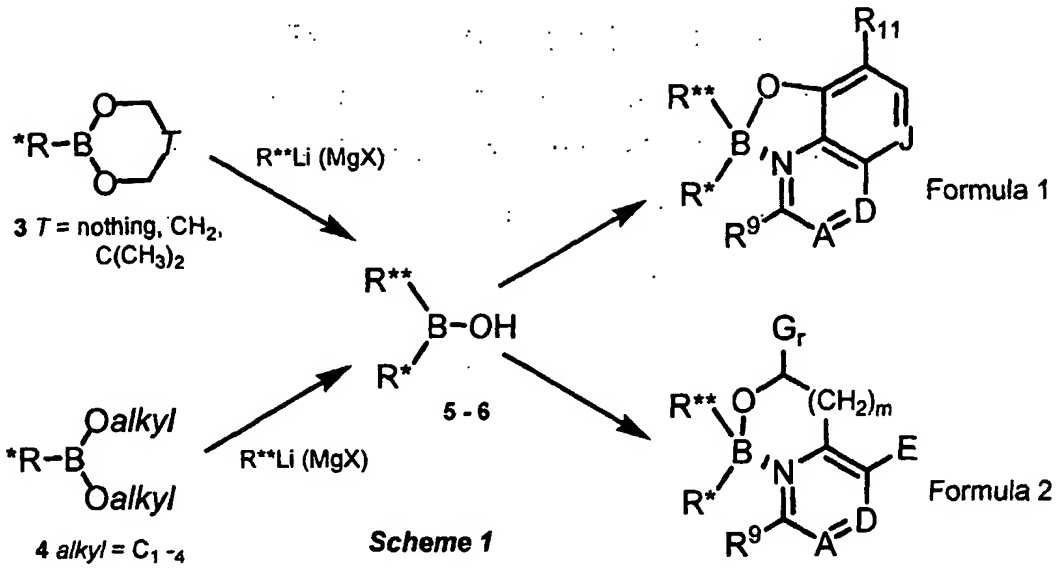
BORINATE COMPLEXES

This procedure was used to obtain the results in the following tables. Representative microbiological data for the compounds 10 to 123 are shown in Tables 1 to 4 as MIC (Minimum Inhibitory Concentration) with the values expressed as micrograms per ml.

Thus, the invention provides antibiotics that are generically called borinic acid complexes, most preferably derived from disubstituted borinic acids.

The synthesis of the compounds of the invention is accomplished in several formats. Reaction scheme #1 demonstrate the synthesis of the intermediate borinic acids, and their subsequent conversion to the desired borinic acid complexes. When R* and R** are identical, the reaction of two equivalents of an arylmagnesium halide (or aryllithium) with trialkyl borate, followed by acidic hydrolysis affords the desired borinic acid **5**. When R* and R** are not identical, the reaction of an equivalent of an arylmagnesium halide (or aryllithium) with appropriate aryl(dialkoxy)borane (**4**), heteroaryl(dialkoxy)borane or alkyl(dialkoxy)borane (alkoxy group comprised of methoxy, ethoxy, isopropoxy, or propoxy moiety), followed by acidic hydrolysis affords the unsymmetrical borinic acids **6** in excellent yields. Where applicable, the reaction of the alkylene esters (**3**, T = nothing, CH_2, CMe_2) with the appropriate organolithium or organomagnesium reactant is convenient.

As shown in Scheme 1, the borinic acid complexes are obtained from the precursor borinic acids by reaction with 1 equivalent of the desired heterocyclic ligand in suitable solvents (i.e., ethanol, isopropanol, dioxane, ether, toluene, dimethylformamide, N-methylpyrrolidone, or tetrahydrofuran).



Scheme 1

In certain situations, compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, *i.e.*, optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

Representative compounds of the present invention include, but are not limited to the compounds disclosed herein and their pharmaceutically acceptable acid and base addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. In a preferred embodiment, the compounds of the invention comprise any of compounds 10 – 123 (Tables 1, 2, 3 and 4), and variants thereof.

Table 1. Antibacterial Profile Against Select Gram-positive and Gram-negative Pathogens

Cmp	R*	R**	Ligand	*S. aureus* ATCC 29213	*S. epidermidis* ATCC 12228	*S. pneumoniae* ATCC 6301	*E. faecalis* ATCC 29212	*E. faecium* CT-26	*M. catarrhalis* ATCC 25238
10	3-ClC_6H_4	3-ClC_6H_4	8-hydroxyquinoline	1	2	2	32	4	NA
11	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	4-hydroxybenzimidazole	0.125	4	NA	8	8	NA
12	3-ClC_6H_4	3-ClC_6H_4	5-fluoro-8-hydroxyquinoline	0.125	2	2	8	4	2
13	3-ClC_6H_4	3-ClC_6H_4	5-chloro-8-hydroxyquinoline	0.125	1	1	64	2	0.25
14	3-ClC_6H_4	3-ClC_6H_4	4-methyl-8-hydroxyquinoline	0.125	1	1	64	4	0.5
15	2-F-4-ClC_6H_3	3-FC_6H_4	8-hydroxyquinoline	0.125	1	2	16	4	0.5
16	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	2-HO_2C-4-hydroxy-5,7-dichloroquinoline	0.25	0.5	NA	0.5	0.25	NA
17	3-ClC_6H_4	3-ClC_6H_4	2-amino-8-hydroxyquinoline	0.25	2	2	8	8	2
18	3-ClC_6H_4	3-Cl-4-FC_6H_3	8-hydroxyquinoline	0.25	1	2	8	4	1
19	3-ClC_6H_4	3-ClC_6H_4	5-cyano-8-hydroxyquinoline	0.25	2	4	16	4	0.5
20	3-ClC_6H_4	3-Cl-5-FC_6H_3	8-hydroxyquinoline	0.25	1	2	8	4	2
21	3-ClC_6H_4	3-FC_6H_4	5-cyano-8-hydroxyquinoline	0.5	4	2	16	8	0.25
22	3-ClC_6H_4	3-FC_6H_4	5-nitro-8-hydroxyquinoline	0.5	4	2	64	16	0.12
23	3-ClC_6H_4	3-FC_6H_4	5-chloro-7-chloro-8-hydroxyquinoline	0.5	16	8	64	16	0.12
24	3-ClC_6H_4	3-FC_6H_4	5-bromo-7-bromo-8-hydroxyquinoline	0.5	8	8	64	32	0.12
25	3-ClC_6H_4	3-ClC_6H_4	2-carboxy-4-hydroxy-8-methoxyquinoline	0.5	8	2	16	16	2
26	2-thienyl	Me	8-hydroxyquinoline	0.5	1	NA	4	4	NA
27	3-NCC_6H_4	4-Me-3-ClC_6H_3	8-hydroxyquinoline	0.5	1	1	8	2	1
28	3,4-$Cl_2C_6H_3$	3-FC_6H_4	8-hydroxyquinoline	0.5	1	2	4	2	1
29	2,4-$Cl_2C_6H_3$	3-FC_6H_4	8-hydroxyquinoline	0.5	1	2	8	2	0.5
30	3,4-$Cl_2C_6H_3$	3,4-$Cl_2C_6H_3$	8-hydroxyquinoline	1	0.5	NA	2	2	NA
31	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	2-carboxy-4-hydroxyquinoline	1	1	NA	2	1	NA
32	3-ClC_6H_4	3-FC_6H_4	8-hydroxyquinoline	1	1	1	16	2	2
33	3-Cl-5-FC_6H_3	3-MeC_6H_4	8-hydroxyquinoline	1	1	1	8	2	2
34	3-ClC_6H_4	3-FC_6H_4	5-fluoro-8-hydroxyquinoline	1	2	2	8	4	1
35	3-ClC_6H_4	3-$MeSC_6H_4$	5-fluoro-8-hydroxyquinoline	1	2	2	8	4	2
36	3-ClC_6H_4	2-thienyl	8-hydroxyquinoline	1	1	2	8	2	4
37	3-Me-4-ClC_6H_3	3-NCC_6H_4	8-hydroxyquinoline	1	1	1	8	2	1
38	2-FC_6H_4	3-NCC_6H_4	8-hydroxyquinoline	1	1	2	16	2	1
39	3-ClC_6H_4	3-NCC_6H_4	8-hydroxyquinoline	1	1	1	8	2	2
40	3-NCC_6H_4	Vinyl	8-hydroxyquinoline	1	1	1	8	2	2

41	3-NCC_6H_4	Ethynyl	8-hydroxyquinoline	1	1	1	4	2	1
42	3-FC_6H_4	Ethynyl	8-hydroxyquinoline	1	1	1	8	2	1
43	2-ClC_6H_4	Ethynyl	8-hydroxyquinoline	1	1	1	8	2	1
44	Ethynyl	Ethynyl	8-hydroxyquinoline	1	1	1	16	2	0.25
45	3,5-$F_2C_6H_3$	Ethynyl	8-hydroxyquinoline	1	1	1	8	1	1
46	3,5-$Cl_2C_6H_3$	Ethynyl	8-hydroxyquinoline	1	1	1	4	1	1
47	3,4-$Cl_2C_6H_3$	Ethynyl	8-hydroxyquinoline	1	1	1	8	2	1
48	3-Cl-4-FC_6H_3	Ethynyl	8-hydroxyquinoline	1	1	1	8	2	2
49	4-ClC_6H_4	4-ClC_6H_4	5-chloro-8-hydroxyquinoline	2	1	1	16	2	0.25
50	4-ClC_6H_4	4-ClC_6H_4	8-hydroxyquinoline	2	2	2	4	4	NA
51	3-FC_6H_4	3-FC_6H_4	8-hydroxyquinoline	2	1	NA	8	2	NA
52	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	8-hydroxyquinoline	2	4	NA	8	16	NA
53	3-NCC_6H_4	3-NCC_6H_4	8-hydroxyquinoline	2	2	NA	64	4	2
54	4-ClC_6H_4	4-Cl-3-FC_6H_3	8-hydroxyquinoline	2	1	2	8	4	1
55	4-Cl-3-FC_6H_3	4-Cl-3-FC_6H_3	8-hydroxyquinoline	2	1	2	4	2	4
56	3-MeC_6H_4	3,5-$Cl_2C_6H_3$	8-hydroxyquinoline	2	2	2	8	4	4
57	4-ClC_6H_4	4-FC_6H_4	5-fluoro-8-hydroxyquinoline	2	2	4	16	4	1
58	3-ClC_6H_4	4-FC_6H_4	5-fluoro-8-hydroxyquinoline	2	2	2	8	4	0.5
59	3-ClC_6H_4	4-$MeSC_6H_4$	8-hydroxyquinoline	2	1	1	8	4	2
60	4-ClC_6H_4	3-$MeSC_6H_4$	8-hydroxyquinoline	2	1	2	8	4	2
61	3-ClC_6H_4	cyclopropyl	8-hydroxyquinoline	2	1	1	16	2	2
62	4-ClC_6H_4	3-$MeSC_6H_4$	5-fluoro-8-hydroxyquinoline	2	2	2	8	4	2
63	4-ClC_6H_4	4-$MeSC_6H_4$	8-hydroxyquinoline	2	1	2	8	4	1
64	4-ClC_6H_4	4-$MeSC_6H_4$	5-fluoro-8-hydroxyquinoline	2	2	4	8	8	1
65	4-ClC_6H_4	4-Cl-3-HOC_6H_3	8-hydroxyquinoline	2	2	2	16	4	4
66	4-ClC_6H_4	3-FC_6H_4	4-methyl-8-hydroxyquinoline	2	1	1	64	4	0.5
67	3-ClC_6H_4	3-(DMISO)C_6H_4	4-methyl-8-hydroxyquinoline	2	1	1	64	4	0.5
68	3-FC_6H_4	3-(DMISO)C_6H_4	8-hydroxyquinoline	2	2	16	32	4	0.12
69	3-(DMISO)C_6H_4	cyclopropyl	8-hydroxyquinoline	2	1	2	64	4	1
70	3-FC_6H_4	cyclopropyl	8-hydroxyquinoline	2	1	1	64	2	0.5
71	3-FC_6H_4	4-NCC_6H_4	5-chloro-7-chloro-8-hydroxyquinoline	2	2	8	64	4	0.12
72	3-(DMISO)C_6H_4	3-(DMISO)C_6H_4	8-hydroxyquinoline	4	2	4	64	4	NA
73	3-(DMISO)C_6H_4	Vinyl	8-hydroxyquinoline	2	1	2	64	8	0.25
74	4-FC_6H_4	4-NCC_6H_4	8-hydroxyquinoline	2	1	2	32	2	1
75	3-ClC_6H_4	3-$MeSC_6H_4$	8-hydroxyquinoline	2	1	2	64	4	NA

76	4-Me-3-ClC$_6$H$_3$	2-thienyl	8-hydroxyquinoline	2	1	NA	8	4	NA
77	3-ClC$_6$H$_4$	2-MeC$_6$H$_4$	8-hydroxyquinoline	2	1	1	8	4	2
78	3-ClC$_6$H$_4$	2-MeOC$_6$H$_4$	8-hydroxyquinoline	2	1	1	8	2	2
79	3-ClC$_6$H$_4$	2-Me-4-ClC$_6$H$_3$	8-hydroxyquinoline	2	2	2	8	4	2
80	4-Cl-3-MeC$_6$H$_3$	4-Cl-3-MeC$_6$H$_3$	8-hydroxyquinoline	2	1	2	4	4	2
81	3-ClC$_6$H$_4$	3-Cl-6-MeOC$_6$H$_3$	8-hydroxyquinoline	2	1	2	8	4	2
82	3,5-Cl$_2$C$_6$H$_3$	4-(Me$_2$NC$_2$H$_4$)OC$_6$H$_4$	8-hydroxyquinoline	2	2	2	8	2	4
83	4-BrC$_6$H$_4$	4-(Me$_2$NC$_2$H$_4$)OC$_6$H$_4$	8-hydroxyquinoline	2	1	2	4	4	2
84	3-ClC$_6$H$_4$	4-F-3-MeC$_6$H$_3$	8-hydroxyquinoline	2	1	2	8	4	4
85	3-Me-4-ClC$_6$H$_3$	3-F-4-ClC$_6$H$_3$	8-hydroxyquinoline	2	1	2	4	4	2
86	3-FC$_6$H$_4$	4-Cl-3-MeC$_6$H$_3$	8-hydroxyquinoline	2	1	2	8	4	2
87	3-FC$_6$H$_4$	3-F-4-ClC$_6$H$_3$	8-hydroxyquinoline	2	1	2	8	4	1
88	3-Cl-6-FC$_6$H$_3$	3-NCC$_6$H$_4$	8-hydroxyquinoline	2	2	2	8	2	2
89	2,5-F$_2$C$_6$H$_3$	3-NCC$_6$H$_4$	8-hydroxyquinoline	2	1	1	8	2	2
90	4-F-3-ClC$_6$H$_3$	3-NCC$_6$H$_4$	8-hydroxyquinoline	2	2	1	8	2	2
91	3-Me-4-ClC$_6$H$_3$	4-NCC$_6$H$_4$	8-hydroxyquinoline	2	1	2	8	2	1
92	2,5-F$_2$C$_6$H$_3$	4-NCC$_6$H$_4$	8-hydroxyquinoline	2	1	2	8	4	1
93	3-Cl-6-FC$_6$H$_3$	4-NCC$_6$H$_4$	8-hydroxyquinoline	2	1	1	8	4	1
94	3-Cl-6-MeOC$_6$H$_3$	4-NCC$_6$H$_4$	8-hydroxyquinoline	2	1	1	8	4	2
95	4-NCC$_6$H$_4$	Ethynyl	8-hydroxyquinoline	2	1	2	8	2	1
96	4-ClC$_6$H$_4$	3,4-F$_2$C$_6$H$_3$	8-hydroxyquinoline	2	1	2	8	2	1
97	4-ClC$_6$H$_4$	4-Me-3-FC$_6$H$_3$	8-hydroxyquinoline	2	1	1	8	2	1
98	4-ClC$_6$H$_4$	3,5-F$_2$C$_6$H$_3$	8-hydroxyquinoline	2	1	1	8	4	1
99	3-CF$_3$-4-ClC$_6$H$_3$	3-FC$_6$H$_4$	8-hydroxyquinoline	2	1	2	8	2	1
100	4-ClC$_6$H$_4$	3-F-5-CF$_3$C$_6$H$_3$	8-hydroxyquinoline	2	1	2	4	2	1
Ciprofloxacin				0.125	0.125	0.5	0.5	64	0.125
Cloxacillin				0.125	0.25	0.125	16	64	1
Imipenem				0.125	0.125	0.125	1	64	0.125
Ceftriaxone				2	1	0.125	64	64	0.125
Meropenem				0.06	0.06		2		
Erythromycin				0.5	0.5		2		
Pen G				0.5	16	0.125	1	32	0.125

DMISO = 4,4-dimethyloxazolin-2-yl

Table 2. Antibacterial Profile Against Select Gram-positive and Gram-negative Pathogens

Cmp	R*	R**	Ligand	*S. aureus* ATCC 29213	*S. epidermidis* ATCC 12228	*S. pneumonia* ATCC 6301	*E. faecalis* ATCC 29212	*E. faecium* CT-26	*H. influenzae* ATCC 49766
101	3-ClC_6H_4	3-ClC_6H_4	1-(2-morpholino-4-yl-ethyl)-imidazoleacetate	0.12	4	16	64	64	4
102	3-ClC_6H_4	3-ClC_6H_4	2-hydroxyisopropyl-3-hydroxypyridine	0.5	1	0.25	64	2	64
103	4-ClC_6H_4	4-ClC_6H_4	2-hydroxyisopropyl-3-hydroxypyridine	0.25	0.5	0.5	4	1	64
104	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	2-hydroxymethyl-1N-benzylimidazole	0.5	4	NA	16	32	8
105	3-ClC_6H_4	3-ClC_6H_4	2-hydroxymethylpyridine	0.125	4	4	32	32	4
106	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	2-pyridylacetic acid	0.5	4	NA	64	64	64
107	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	3-(2-hydroxyethoxy)picolinic acid	0.125	4	NA	16	8	32
108	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	3-(N-morpholinylethoxy)picolinic acid	0.25	4	NA	4	2	64
109	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	3-($OCH_2CH_2CH_2CO_2H$)picolinic acid	1	4	4	32	16	16
110	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	3-carboxypicolinic acid	0.125	4	NA	8	8	8
111	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	3-hydroxypicolinic acid	2	1	NA	2	2	64
112	4-Me-3-ClC_6H_3	4-$CH_3C_6H_4$	3-hydroxypicolinic acid	4	2	NA	4	8	64
113	4-Me-3-ClC_6H_3	Phenylethyl	3-hydroxypicolinic acid	0.5	1	NA	2	64	64
114	3-ClC_6H_4	3-ClC_6H_4	3-hydroxypicolinic acid	0.125	8	NA	64	64	16
115	4-EtO-3-ClC_6H_3	4-EtO-3-ClC_6H_3	3-hydroxypicolinic acid	2	2	1	8	16	64
116	2-Cl-5-Br-6-FC_6H_2	2-F-4-ClC_6H_3	3-hydroxypicolinic acid	2	1	0.25	4	4	64
117	2-Me-4-ClC_6H_3	3-ClC_6H_4	3-hydroxypicolinic acid	2	1	0.5	4	4	16
118	2-Me-4-ClC_6H_3	2-Me-4-ClC_6H_3	3-hydroxypicolinic acid	1	0.25	0.12	1	1	16
119	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	3-OAc-picolinic acid	2	1	NA	2	2	64
120	4-Me-3-ClC_6H_3	4-Me-3-ClC_6H_3	4-hydroxybenzimidazole	0.125	4	NA	8	8	
121	3-ClC_6H_4	3-ClC_6H_4	4–hydroxyethylimidazole	0.125	4	8	32	32	4
122	3-ClC_6H_4	3-ClC_6H_4	6-amino-3-hydroxypicolinic acid	0.25	4	16	32	32	8
123	3-ClC_6H_4	3-ClC_6H_4	Imidazole acetic acid	0.125	2	8	32	32	8
Ceftriaxone				2	1	<0.125	64	64	0.12
Ciprofloxacin				0.12	0.12	0.5	0.5	64	0.12
Cloxacillin				0.12	0.25	0.12	16	64	8
Erythromycin				0.5	0.5	NA	2	NA	4
Imipenem				0.12	0.12	<0.125	1	64	2
Meropenem				0.06	0.06	NA	2	NA	0.06
Pen G				0.5	16	<0.125	1	32	0.12

Table 3. Anti-mycobacterium In vitro Activity			
	M. tuberculosis MIC (mcg/mL)		
Compound	**H37Rv***	**P2SP1****	**P1SP2****
10	0.387	0.387	0.387
50	0.387	0.387	0.387
51	0.387	0.387	0.387
53	0.775	0.775	0.387
55	0.775	0.775	0.387
65	0.775	0.775	0.775
72	0.775	0.775	0.775
75	0.775	0.775	0.775
Isoniazid (INH)	<0.062	>8	>8
Rifampicin	<0.125	16	>16
Ethambutol	<1	8	8
Ethionamide	1	>64	32
p-aminosalicylate	<0.25	32	16
Ofloxacin	4	32	16
Streptomycin	<2	<2	<2
Kanamycin	<2	<2	<2
cycloserine	8	8	8
*Sensitive strain **Multi-drug resistant strain			

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Table 4.

Antifungal Activity for Select Borinic Acid Complexes

Compound	*C. albicans* ATCC 90028
10	2
50	2
51	1
52	2
53	1
55	1
65	0.5
72	4
76	2

10

The present invention also encompasses the acylated prodrugs of the compounds of the invention. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the inventive compounds.

Tables 1, 2 and 3 also contain inhibitory activity for known antibiotics, shown at the end of each of the tables.

EXAMPLES

Proton NMR are recorded on Varian AS 400 spectrometer and chemical shifts are reported as δ (ppm) down field from tetramethylsilane. Mass spectra are determined on Micromass Quattro II. Example numbers refer to compounds.

Formation of ethylene glycol boronate ester (Compound 3, *T* = nothing)

General procedure

Boronic acid was dissolved in dry THF or dry diethyl ether (~10 mL/g) under nitrogen. Ethylene glycol (1 molar equivalent) was added to the reaction and the reaction was heated to reflux for 1 to 4 hours. Reaction was cooled to room temperature and solvent was removed under reduced pressure leaving the ethylene glycol ester as an oil or a solid. In cases where an oil was obtained or a solid that dissolved in hexane, dry hexane was added and removed under reduced pressure. The product was then placed under high vacuum for several hours. In cases where a solid was obtained that did not dissolve in hexane, the solid was collected by filtration and washed with cold hexane.

3-Cyanophenylboronic acid ethylene glycol ester (3a)

3-Cyanophenyl boronic acid (1 g, 6.8 mmol) was dissolved in dry THF (10 mL) under nitrogen. Ethylene glycol (379 µL, 422 mg, 6.8 mmol) was added and

the reaction was heated to reflux for 4 hours then cooled to room temperature. THF was removed by rotary evaporator to give a white solid. Cold hexane was added and the product was collected by filtration giving a white solid (1.18 g, quant. yield). ^{1}H-NMR (300.058 MHz, DMSO-d6) δ ppm 7.92-8.01 (3H, m), 7.50-7.64 (1H, m), 4.35 (4H, s)

Thiophene 3-boronic acid ethylene glycol ester (3b)

Thiophen-3-boronic acid (1 g, 7.8 mmol) was dissolved in dry THF (10 mL) under nitrogen. Ethylene glycol (435 μL, 484 mg, 7.8 mmol) was added and the reaction was heated to reflux for 1 hour then cooled to room temperature. THF was removed by rotary evaporator to give a white solid. Hexane was added, dissolving the solid and removed by rotary evaporation. The product was placed under high vacuum to yield a tan solid (1.17g, 97%). ^{1}H-NMR (300.058 MHz, $CDCl_3$) δ ppm 7.93 (1H, s), 7.3-7.4 (2H, m), 4.35 (4H, s).

Formation of unsymmetrical borinic acid (6) from boronic acid ethylene glycol ester

General procedure A: Grignard methodology

Boronic acid ethylene glycol ester was dissolved in dry THF (10-20 mL/g) under nitrogen. Solution was cooled to -78 °C in an acetone/dry ice bath or to 0 °C in an ice/water bath. Grignard reagent (0.95 to 1.2 molar equivalent) was added dropwise to the cooled solution. The reaction was warmed to room temperature and stirred for 3-18 hours. 6N HCl (2 mL/g) was added and solvent was removed under reduced vacuum. Product was extracted into diethyl ether (40 mL/g) and washed with water (3 x equal volume). Organic layer was dried ($MgSO_4$), filtered and the solvent was removed by rotary evaporation giving the crude product, which is either purified by column chromatography or taken onto the next step without purification. Alternative work-up: if the borinic acid product contained a basic group such as an amine or pyridine, then after stirring at room temperature for 3 – 18 hours water (2

mL/g) was added and the pH adjusted to 5-7. Product was extracted into diethyl ether (40 mL/g) and washed with water (3 x equal volume). Organic layer was dried ($MgSO_4$), filtered and the solvent was removed by rotary evaporation giving the crude product, which is either purified by column chromatography or taken onto the next step without purification.

(4-Cyanophenyl)(3-fluorophenyl)borinic acid (6a)

4-Cyanophenyl boronic acid ethylene glycol ester (500 mg, 2.89 mmol) was dissolved in dry THF under nitrogen. The solution was cooled to -78 °C in an acetone/dry ice bath and 3-fluorophenylmagnesium bromide (1M in THF)(2.74 mL, 2.74 mmol, 0.95 molar equivalent) was added dropwise to the cold solution. The reaction was allowed to warm slowly to room temperature and stirred for 18 hours. 6N HCl (1 mL) was added to the reaction causing a cloudy appearance and the solvent was removed using a rotary evaporator. The product was extracted into diethyl ether (20 mL) and washed with water (3 x 20 mL). The organic layer was dried (MgSO4), filtered and the solvent removed using a rotary evaporator to yield the crude product as an oily solid. This was taken onto the next step without purification.

General procedure B: (Hetero)aryl-lithium methodology

The (hetero)aryl-bromide or iodide was dissolved in dry THF (20-30 mL/g) under nitrogen and degassed. The solution was cooled to -78 °C in an acetone/dry ice bath and n-, sec- or tert-butyllithium in THF or other solvent (1.5-2.4 molar equivalents) was added to the cooled solution dropwise generally causing the solution to turn deep yellow. The boronic acid ethylene glycol ester (1 molar equivalent) was dissolved in dry THF or diethyl ether (2-5 mL/g) under nitrogen. The boronic acid ethylene glycol ester in THF was added dropwise to the cooled aryl-lithium solution generally causing the solution to turn pale yellow. The reaction was warmed to room temperature and stirred for 3-18 hours. 6N HCl (2-4 mL/g) was added and solvent was removed under reduced vacuum. Product was extracted into diethyl ether (40 mL/g) and washed with water (3 x equal volume). Organic layer was dried

($MgSO_4$), filtered and the solvent was removed by rotary evaporation giving the crude product, which is either purified by column chromatography or taken onto the next step without purification. Alternative work-up: if the borinic acid product contained a basic group such as an amine or pyridine then after stirring at room temperature for 3 – 18 hours water (2 mL/g) was added and the pH adjusted to 5-7. Product was extracted into diethyl ether (40 mL/g) and washed with water (3 x equal volume). Organic layer was dried ($MgSO_4$), filtered and the solvent was removed by rotary evaporation giving the crude product, which is either purified by column chromatography or taken onto the next step without purification.

(3-Thiophene)(3-chlorophenyl)borinic acid (6b)

3-Chloro-bromobenzene (447 μL, 728 mg, 3.8 mmol) was dissolved in dry THF (15 mL) under nitrogen. The solution was degassed and cooled to -78 °C in an acetone/dry ice bath. tert-Butyllithium (1.7M in THF)(4.47 mL, 7.6 mmol, 2 molar equivalent) was added to the cooled solution dropwise causing the solution to turn deep yellow. The solution was stirred at -78 °C while 3-thiopheneboronic acid ethylene glycol ester (586 mg) was dissolved in dry diethyl ether (1 mL). The boronic ester solution was then added dropwise to the cooled solution causing the colour to change to pale yellow. The reaction was warmed to room temperature and stirred for 18 hours. 6N HCl (2 mL) was added and the reaction was stirred for 1 hour. The solvent was removed using a rotary evaporator. The product was extracted into diethyl ether (10 mL) and washed with water (2 x 10 mL). The organic layer was dried (MgSO4), filtered and the solvent removed using a rotary evaporator to yield the crude product as an orange oil. The product was purified by column chromatography using silica gel and hexane:ethyl acetate 5:1 as eluent giving the pure product as a clear oil (614 mg, 73%).

(3-Chlorophenyl)vinylborinic acid (6c)

This was prepared by a similar process as described for 6b by the reaction of 3-cyanophenyl boronic acid ethylene glycol ester with vinyllithium.

(3-Fluoro-5-chlorophenyl)ethynylborinic acid (6d)

This was prepared by a similar process as described for 6b by the reaction of 3-fluoro-5-chlorophenyl boronic acid ethylene glycol ester with ethynyllithium.

(4-Methyl-3-chlorophenyl)(2-thienyl)borinic acid (6e)

This was prepared by a similar process as described for 6b by the reaction of 2-thienylboronic acid ethylene glycol ester with 4-methyl-3-chlorophenyllithium..

(4-Cyanophenyl)ethynylborinic acid (6f)

This was prepared by a similar process as described for 6b by the reaction of 4-cyanophenylboronic acid ethylene glycol ester with ethynyllithium.

(3-Fluorophenyl)cyclopropylborinic acid (6g)

This was prepared by a similar process as described for 6b by the reaction of 3-fluorophenylboronic acid ethylene glycol ester with cyclopropyllithium.

(3-Thienyl)methylborinic acid (6h)

This was prepared by a similar process as described for 6b by the reaction of 3-thienylboronic acid ethylene glycol ester with methyllithium.

(4-Pyridyl)phenylborinic acid (6i)

This was prepared by a similar process as described for 6b by the reaction of phenylboronic acid ethylene glycol ester with 4-pyridyllithium.

(3-Cyanophenyl)(2-fluorophenyl)borinic acid (6j)

This was prepared by a similar process as described for 6b by the reaction of 3-cyanophenylboronic acid ethylene glycol ester with 2-fluorophenyllithium.

Formation of symmetrical borinic acid (5) by reaction of organometallics with trialkyl borates. Bis(4-chlorophenyl)borinic acid (5a) (Procedure C)

A cold solution (-78 °C) of trimethyl borate (0.37 ml) in dry tetrahydrofuran (THF, 25 ml) was treated dropwise with 4-chlorophenylmagnesium bromide (6.75 ml, 1M solution in ether). The reaction mixture was stirred at -78 °C for 1 h and then stirred for 18 h at room temperature. The solvent was removed under reduced pressure. The resultant residue was stirred with 100 ml of ether and 15 ml of 6N hydrochloric acid. Organic layer was separated and aqueous layer was extracted with ether (2 X 100 ml). The combined organic extract was washed with brine and dried over anhydrous magnesium sulfate. Solvent was removed to give light yellowish solid. The product was chromatographed over silica gel (Hex: Ether =1:1) to give 420 mg of borinic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (s, OH), 7.46 (d, 4H, Ar-H), 7.72 (d, 4H, Ar-H).

Bis(3-Chloro-4-methylphenyl)borinic acid (5b)

In a similar manner as for 5a, the titled compound was obtained from the reaction of 3-chloro-4-methylphenylmagnesium bromide with trimethyl borate. The product was obtained by chromatography over silica gel.

Bis(3-Fluoro-4-methylphenyl)borinic acid (5c)

In a similar manner as for 5a, the titled compound was obtained from the reaction of 3-fluoro-4-methylphenyllithium with trimethyl borate. The product was obtained by chromatography over silica gel.

Bis(3-Chloro-4-methoxyphenyl)borinic acid (5d)

In a similar manner as for 5a, the titled compound was obtained from the reaction of 3-chloro-4-methoxyphenyllithium with trimethyl borate. The product was obtained by chromatography over silica gel.

Bis(3-Fluoro-4-methoxyphenyl)borinic acid (5e)

In a similar manner as for 5a, the titled compound was obtained from the reaction of 3-fluoro-4-methoxyphenyllithium with trimethyl borate. The product was obtained by chromatography over silica gel.

Formation of unsymmetrical borinic acids (6) by reaction of organometallics with alkyl(aryl)dialkoxyboranes. (4-Chlorophenyl)methyl-borinic acid (6k) (Procedure D)

To 4-chlorophenylmagnesium bromide (5.5 ml; 1M solution in ether) at -78 °C, di(isopropoxy)methylborane (1 ml, 0.78 g) was added dropwise via syringe. The reaction mixture was stirred at -78 °C for 1h and then stirred overnight at ambient temperature. The reaction mixture was treated dropwise with 100 ml of ether and 15 ml of 6N hydrochloric acid, and stirred for 1 h. Organic layer was separated and aqueous layer was extracted with ether (2 X 100 ml). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. Solvent was removed under reduce pressure to give 1.1 g of oil. ^{1}H NMR of the product was consistent for (4-chlorophenyl)methyl borinic acid.

(4-Fluorophenyl)methylborinic acid (6m)

In a similar manner as for 6k, the titled compound was obtained from the reaction of 4-fluorophenylmagnesium bromide with di(isopropoxy)methylborane. The product was obtained by chromatography over silica gel.

(4-Biphenyl)methylborinic acid (6n)

In a similar manner as for 6k, the titled compound was obtained from the reaction of 4-biphenyllithium with di(isopropoxy)methylborane. The product was obtained by chromatography over silica gel.

(3-Chloro-4-methylphenyl)methylborinic acid (6o)

In a similar manner as for 6k, the titled compound was obtained from the reaction of 3-chloro-4-methylphenyllithium with di(isopropoxy)methylborane. The product was obtained by chromatography over silica gel.

(3-Chloro-4-methoxyphenyl)methylborinic acid (6p)

In a similar manner as for 6k, the titled compound was obtained from the reaction of 3-chloro-4-methoxyphenyllithium with di(isopropoxy)methylborane. The product was obtained by chromatography over silica gel.

(4-Dimethylaminophenyl)methylborinic acid (6q)

In a similar manner as for 6k, the titled compound was obtained from the reaction of 4-dimethylaminophenyllithium with di(isopropoxy)methylborane. The product was obtained by chromatography over silica gel.

(3-Chloro-4-dimethylaminophenyl)vinylborinic acid (6r)

In a similar manner as for 6k, the titled compound was obtained from the reaction of 3-chloro-4-dimethylaminophenyllithium with di(butoxyvinyl)-borane. The product was obtained by chromatography over silica gel.

Bis(3-Chlorophenyl)borinic acid 4-(hydroxyeethyl)imidazole ester (121)

To a solution of bis(3-chlorophenyl)borinic acid (0.4 g, 1.428 mmol) in ethanol (10 ml), 4-(hydroxyethyl)imidazole hydrochloride (0.191 g, 1.428 mmol), sodium bicarbonate (0.180 g, 2.143 mmol) were added and the reaction mixture was stirred at room temperature for 18 h. Salt was removed by filtration. Filtrate was concentrated and treated with hexane to afford the product as a solid and was collected by filtration. (450 mg, 84.9% yield)

Bis(4-Chlorophenyl)borinic acid 4-(hydroxymethyl)imidazole ester (126)

In a similar manner as in Example 121, the titled compound was obtained from the reaction of bis(4-chlorophenyl)borinic acid with 4-(hydroxymethyl)imidazole hydrochloride. The product was obtained as white crystals.

Bis(3-Chloro-4-methylphenyl)borinic acid 1-benzyl-4-(hydroxymethyl)-imidazole ester (127)

To a solution of 1-benzyl-4-(hydroxymethyl)imidazole (96 mg, 0.521 mmol) in methanol (5 ml), bis(3-chloro-4-methylphenyl)borinic acid (121 mg, 0.521 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. Solvent was removed under reduced pressure and the residue was treated with hexane to give a solid. The product was isolated by filtration and washed with hexane to give product (193 mg, 83%). ^{1}H NMR ($CDCl_3$) δ: 2.3 (s, 6H, 2XCH_3), 4.8 (brs, 2H, CH_2), 5.1 (brs, 2H, CH_2), 6.9-7.4 (complex, 13H, Ar-H); MS (ES^+)(m/z) 448.78, MF $C_{25}H_{23}BCl_2N_2O$.

Bis(3-Chloro-4-methylphenyl)borinic acid 1-methyl-2-(hydroxymethyl)-imidazole ester (128)

In a similar manner as in Example 127, the titled compound was obtained from the reaction of bis(3-chloro-4-methylphenyl)borinic acid with 1-methyl-2-

(hydroxy-methyl)imidazole hydrochloride. The product was obtained as white crystals.

Bis(3-Chloro-4-methylphenyl)borinic acid 1-ethyl-2-(hydroxymethyl)-imidazole ester (129)

In a similar manner as in Example 127, the titled compound was obtained from the reaction of bis(3-chloro-4-methylphenyl)borinic acid with 1-ethyl-2-(hydroxy-methyl)imidazole hydrochloride. The product was obtained as white crystals.

Bis(3-Chloro-4-methylphenyl)borinic acid 1-methyl-4-(hydroxymethyl)-imidazole ester (130)

In a similar manner as in Example 127, the titled compound was obtained from the reaction of bis(3-chloro-4-methylphenyl)borinic acid with 1-methyl-4-(hydroxy-methyl)imidazole hydrochloride. The product was obtained as white crystals.

Bis(3-Chloro-4-methylphenyl)borinic acid 2-pyridylethanol (131

In a similar manner as in Example 121, the titled compound was obtained from the reaction of bis(3-chloro-4-methylphenyl)borinic acid with 2-pyridylethanol. The product was obtained as white crystals.

Bis(4-Chlorophenyl)borinic acid 2-pyridylmethanol (132)

In a similar manner as in Example 121, the titled compound was obtained from the reaction of bis(4-chlorophenyl)borinic acid with 2-pyridylmethanol. The product was obtained as white crystals.

Bis(4-Fluorophenyl)borinic acid 2-pyridylmethanol (133)

In a similar manner as in Example 121, the titled compound was obtained from the reaction of bis(4-fluorophenyl)borinic acid with 2-pyridylmethanol. The product was obtained as white crystals.

HYDROXYQUINOLINE DERIVATIVES

Bis(3-Chlorophenyl)borinic acid 8-hydroxyquinoline ester (10)

A solution of bis(3-chlorophenyl)borinic acid (0.18 g) in ethanol (1 ml) and 8-hydroxyquinoline (0.105 g) was stirred at 5 °C. The reaction mixture was then stirred at ambient temperature, and a yellow solid precipitate formed. The reaction mixture was stirred for additional four hours. The product was isolated by filtration, washed with hexane and air dried to give 160 mg of complex.

Bis(3-Chlorophenyl)borinic acid 5-Fluoro-8-hydroxyquinoline ester (12)

In a similar manner as in Example 10, the titled compound was obtained from the reaction of bis(3-chlorophenyl)borinic acid with 5-fluoro-8-hydroxyquinoline. The product was obtained as yellow crystals.

Bis(3-Chlorophenyl)borinic acid 5-chloro-8-hydroxyquinoline ester (13)

In a similar manner as in Example 10 the titled compound was obtained from the reaction of bis(3-chlorophenyl)borinic acid with 5-chloro-8-hydroxyquinoline.. The product was obtained as yellow crystals.

Bis(3-Chlorophenyl)borinic acid 5-cyano-8-hydroxyquinoline ester (19)

In a similar manner as in Example 10, the titled compound was obtained from the reaction of bis(3-chlorophenyl)borinic acid with 5-cyano-8-hydroxyquinoline. The product was obtained as yellow crystals.

(2-Thienyl)methylborinic acid 8-hydroxyquinoline ester (26)

In a similar manner as in Example 10, the titled compound was obtained from the reaction of (2-thienyl)methylborinic acid with 8-hydroxyquinoline. The product was obtained as yellow crystals.

(3-Chlorophenyl)(2-thienyl)borinic acid 8-hydroxyquinoline ester (36

In a similar manner as in Example 10, the titled compound was obtained from the reaction of (3-chlorophenyl)(2-thienyl)borinic acid with 8-hydroxyquinoline. The product was obtained as yellow crystals.

(3-Cyanophenyl)vinylborinic acid 8-hydroxyquinoline ester (40)

In a similar manner as in Example 10, the titled compound was obtained from the reaction of (3-cyanophenyl)vinylborinic acid with 8-hydroxyquinoline. The product was obtained as yellow crystals.

(2-Chlorophenyl)ethynylborinic acid 8-Hydroxyquinoline ester (43)

In a similar manner as in Example 10, the titled compound was obtained from the reaction of (2-chlorophenyl)ethynylborinic acid with 8-hydroxyquinoline. The product was obtained as yellow crystals.

Bis(ethynyl)borinic acid 8-Hydroxyquinoline (44) (XXI)

In a similar manner as in Example 10, the titled compound was obtained from the reaction of bis(ethynyl)borinic acid with 8-hydroxyquinoline. The product was obtained as light yellow crystals.

(3-Fluorophenyl)cyclopropylborinic acid 8-hydroxyquinoline ester (70)

In a similar manner as in Example 10, the titled compound was obtained from the reaction of (3-fluorophenyl)cyclopropylborinic acid with 8-hydroxyquinoline. The product was obtained as light yellow crystals.

In a preferred embodiment, the present invention includes the compounds specifically recited herein, and pharmaceutically acceptable salts thereof, and compositions of any of these compounds where these comprise a pharmaceutically acceptable carrier. Most preferred are compounds having the structure of any of the compounds listed in Tables 1, 2, 3 or 4, especially those having the structure of compound 10 to 108, compound 111-112, or compound 116-120. In such compounds, the ligand is as described elsewhere herein, where the ligand is attached to the boron through the indicated reactive groups.

The present invention also relates to a method for treating a microbial-caused disease in a patient afflicted therewith and/or preventing such infection in a patient at risk of becoming so-infected, comprising administering to said patient a therapeutically effective amount of any of the compounds of the invention, preferably one or more of those listed in Tables 1 to 4. In one aspect, the compounds of the invention have anti-bacterial (i.e., bactericidal) and anti-fungal (i.e., fungicidal) activity.

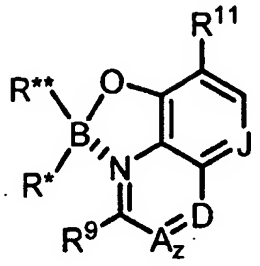
In a preferred embodiment, the microbe is a bacterium, preferably a gram positive bacterium, wherein said gram positive bacterium is a member selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Bacillus* species, *Mycobacterium* species, *Corynebacterium* species, *Clostridium* species, *Actinomyces* species, *Enterococcus* species, and *Streptomyces* species.

In another preferred embodiment of such method, the bacterium is a gram negative bacterium, preferably one selected from the group consisting of *Acinetobacter* species, *Neisseria* species, *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species, *Streptobacillus* species, spirochetal species, *Campylobacter* species, *Vibrio* species, and *Helicobacter* species.

In a highly preferred embodiment of the present invention, the bacterium is a member selected from the group consisting of *Staphylococcus aureus*; *Staphylococcus epidermidis*; *Staphylococcus saprophyticus*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Enterococcus faecalis*; *Enterococcus faecium*; *Bacillus anthracis*; *Mycobacterium avium; Mycobacterium tuberculosis; Acinetobacter baumanii*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *Neisseria gonorrhoeae*; *Neisseria meningitidis*; *Pseudomonas aeruginosa*; *Legionella pneumophila*; *Escherichia coli*; *Yersinia pestis*; *Haemophilus influenzae*; *Helicobacter pylori*; *Campylobacter fetus*; *Campylobacter jejuni; Vibrio cholerae*; *Vibrio parahemolyticus*; *Trepomena pallidum*; *Actinomyces israelii*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus*; *Agrobacterium tumefaciens*; and *Francisella tularensis*.

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula 1



Formula 1

wherein B is boron, O is oxygen

wherein R* and R** are each independently selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 - C_6), substituted or unsubstituted vinyl, substituted or unsubstituted alkynyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, and substituted or unsubstituted heterocycle,

and wherein z is 0 or 1 and when z is 1, A is CH, CR^{10} or N,

and wherein D is N, CH, or CR^{12},

and wherein E is H, OH, alkoxy or N-(morpholinyl)ethoxy

and wherein m is 1 or 2, and wherein when m is 1, G is =O (double-bonded oxygen) and when m is 2, each G is independently H, methyl, ethyl or propyl,

wherein R^{12} is selected from $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2*-amino, 3*-amino, NH_2SO_2 and $CONH_2$,

and wherein J is CR^{10} or N

and wherein R^9, R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, alkyl, $(CH_2)_nOH$ (n = 1, 2 to 3), CH_2NH_2,

$CH_2NHalkyl$, $CH_2N(alkyl)_2$, halogen, CHO, CH=NOH, CO_2H, CO_2-alkyl, S-alkyl, SO_2-alkyl, S-aryl, NH_2, alkoxy, CF_3, SCF_3, NO_2, SO_3H and OH,

including salts thereof.

2. The compound of claim 1 wherein one of R* and R** is a substituted or unsubstituted alkyl (C_1 - C_4).

3. The compound of claim 1 wherein R* and R** are each a substituted or unsubstituted alkyl (C_1 - C_4).

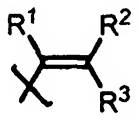
4. The compound of claim 1 wherein one of R* and R** is a substituted or unsubstituted cycloalkyl (C_3 - C_6).

5. The compound of claim 1 wherein R* and R** are each a substituted or unsubstituted cycloalkyl (C_3 - C_6).

6. The compound of claim 1 wherein one of R* and R** is a substituted or unsubstituted vinyl.

7. The compound of claim 1 wherein R* and R** are each a substituted or unsubstituted vinyl.

8. The compound of claim 6 or 7 wherein said vinyl has the structure

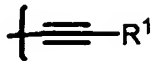


wherein R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

9. The compound of claim 1 wherein one of R* and R** is a substituted or unsubstituted alkynyl.

10. The compound of claim 1 wherein R* and R** are each a substituted or unsubstituted alkynyl.

11. The compound of claim 9 or 10 wherein said alkynyl has the structure

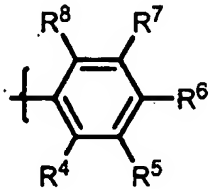


wherein R^1 is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

12. The compound of claim 1 wherein one of R* and R** is a substituted or unsubstituted phenyl.

13. The compound of claim 1 wherein R* and R** are each a substituted or unsubstituted phenyl.

14. The compound of claim 12 or 13 wherein said phenyl has the structure



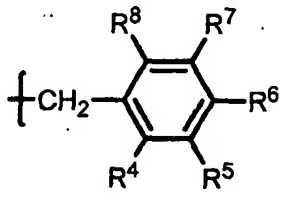
wherein R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl,

substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2°-amino, 3°-amino, NH_2SO_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

15. The compound of claim 1 wherein one of R* and R** is a substituted or unsubstituted benzyl.

16. The compound of claim 1 wherein R* and R** are each a substituted or unsubstituted benzyl.

17. The compound of claim 15 or 16 wherein said benzyl has the structure

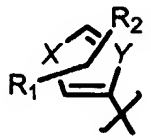


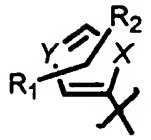
wherein R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2°-amino, 3°-amino, NH_2SO_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

18. The compound of claim 1 wherein one of R* and R** is a substituted or unsubstituted heterocycle.

19. The compound of claim 1 wherein R* and R** are each a substituted or unsubstituted heterocycle.

20. The compound of claim 18 or 19 wherein said heterocycle has the structure



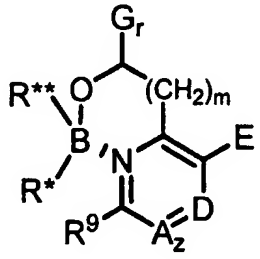
or


wherein X = CH=CH, N=CH, NR^{13} (wherein R^{13} = H, alkyl, aryl or benzyl), O, or S

and wherein Y = CH or N

and wherein R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

21. A compound having the structure of Formula 2



Formula 2

wherein B is boron, O is oxygen, m is 0, 1, or 2,

wherein R* and R** are each independently selected from substituted or unsubstituted alkyl (C_1 - C_4), substituted or unsubstituted cycloalkyl (C_3 -

C_6), substituted or unsubstituted vinyl, substituted or unsubstituted alkynyl, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, and substituted or unsubstituted heterocycle,

and wherein z is 0 or 1 and when z is 1, A is CH, CR^{10} or N,

and wherein D is N, CH, or CR^{12},

and wherein E is H, OH, alkoxy or N-(morpholinyl)ethoxy

and wherein r is 1 or 2, and wherein when r is 1, G is =O (double-bonded oxygen) and when r is 2, each G is independently H, methyl, ethyl or propyl,

wherein R^{12} is selected from $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2*-amino, 3*-amino, NH_2SO_2 and $CONH_2$,

and wherein J is CR^{10} or N

and wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen, alkyl, $(CH_2)_nOH$ (n = 1, 2 or 3), CH_2NH_2, CH_2NHalkyl, $CH_2N(alkyl)_2$, halogen, CHO, CH=NOH, CO_2H, CO_2-alkyl, S-alkyl, SO_2-alkyl, S-aryl, NH_2, alkoxy, CF_3, SCF_3, NO_2, SO_3H and OH,

including salts thereof.

22. The compound of claim 21 wherein one of R* and R** is a substituted or unsubstituted alkyl (C_1 - C_4).

23. The compound of claim 21 wherein R* and R** are each a substituted or unsubstituted alkyl (C_1 - C_4).

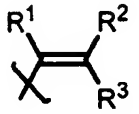
24. The compound of claim 21 wherein one of R* and R** is a substituted or unsubstituted cycloalkyl (C_3 - C_6).

25. The compound of claim 21 wherein R* and R** are each a substituted or unsubstituted cycloalkyl (C_3 - C_6).

26. The compound of claim 21 wherein one of R* and R** is a substituted or unsubstituted vinyl.

27. The compound of claim 21 wherein R* and R** are each a substituted or unsubstituted vinyl.

28. The compound of claim 26 or 27 wherein said vinyl has the structure

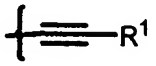


wherein R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

29. The compound of claim 21 wherein one of R* and R** is a substituted or unsubstituted alkynyl.

30. The compound of claim 21 wherein R* and R** are each a substituted or unsubstituted alkynyl.

31. The compound of claim 29 or 30 wherein said alkynyl has the structure



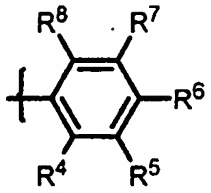
wherein R^1 is selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or

3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

32. The compound of claim 21 wherein one of R* and R** is a substituted or unsubstituted phenyl.

33. The compound of claim 21 wherein R* and R** are each a substituted or unsubstituted phenyl.

34. The compound of claim 32 or 33 wherein said phenyl has the structure

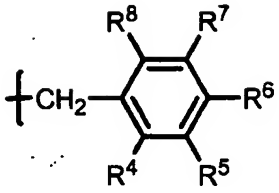


wherein R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2°-amino, 3°-amino, NH_2SO_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

35. The compound of claim 21 wherein one of R* and R** is a substituted or unsubstituted benzyl.

36. The compound of claim 21 wherein R* and R** are each a substituted or unsubstituted benzyl.

37. The compound of claim 35 or 36 wherein said benzyl has the structure

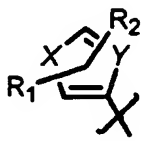


wherein R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, NH_2, 2°-amino, 3°-amino, NH_2SO_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

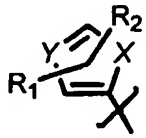
38. The compound of claim 21 wherein one of R* and R** is a substituted or unsubstituted heterocycle.

39. The compound of claim 21 wherein R* and R** are each a substituted or unsubstituted heterocycle.

40. The compound of claim 38 or 39 wherein said heterocycle has the structure



or



wherein X = CH=CH, N=CH, NR^{13} (wherein R^{13} = H, alkyl, aryl or benzyl), O, or S

and wherein Y = CH or N

and wherein R^1, R^2, and R^3 are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, benzyl, substituted benzyl, $(CH_2)_kOH$ (where k = 1, 2 or 3), CH_2NH_2, CH_2NH-alkyl, $CH_2N(alkyl)_2$, CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

41. A compound having the structure of compound 10 to 108, compound 111-112, or compound 116-120.

42. A composition comprising a compound of claim 1 or 21 in a pharmaceutically acceptable carrier.

43. A method for treating a microbial-caused disease in a patient afflicted therewith comprising administering to said patient a therapeutically effective amount of a compound of claim 1 or 21.

44. The method of claim 43 wherein said microbe is a bacterium.

45. The method of claim 44 wherein said bacterium is a gram positive bacterium.

46. The method of claim 45 wherein said gram positive bacterium is a member selected from the group consisting of *Staphylococcus* species, *Streptococcus* species, *Bacillus* species, *Mycobacterium* species, *Corynebacterium* species, *Clostridium* species, *Actinomyces* species, *Enterococcus* species, and *Streptomyces* species;

47. The method of claim 44 wherein said bacterium is a gram negative bacterium.

48. The method of claim 47 wherein said gram negative bacterium is a member selected from the group consisting of *Acinetobacter* species, *Neisseria* species, *Pseudomonas* species, *Brucella* species, *Agrobacterium* species, *Bordetella* species, *Escherichia* species, *Shigella* species, *Yersinia* species, *Salmonella* species, *Klebsiella* species, *Enterobacter* species, *Haemophilus* species, *Pasteurella* species, *Streptobacillus* species, spirochetal species, *Campylobacter* species, *Vibrio* species, and *Helicobacter* species.

49. The method of claim 44 wherein said bacterium is a member selected from the group consisting of *Staphylococcus aureus*; *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*; *Streptococcus pyogenes*; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Enterococcus faecalis*; *Enterococcus faecium*; *Bacillus anthracis*; *Mycobacterium avium*; *Mycobacterium tuberculosis*, *Acinetobacter baumanii*; *Corynebacterium diphtheria*; *Clostridium perfringens*; *Clostridium botulinum*; *Clostridium tetani*; *Neisseria gonorrhoeae*; *Neisseria meningitidis*; *Pseudomonas aeruginosa*; *Legionella pneumophila*; *Escherichia coli*; *Yersinia pestis*; *Haemophilus influenzae*; *Helicobacter pylori*; *Campylobacter fetus*; *Vibrio cholerae*; *Vibrio parahemolyticus*; *Trepomena pallidum*; *Actinomyces israelii*; *Rickettsia prowazekii*; *Rickettsia rickettsii*; *Chlamydia trachomatis*; *Chlamydia psittaci*; *Brucella abortus*; *Agrobacterium tumefaciens*; and *Francisella tularensis*.

50. A method for treating a fungus- or yeast-caused disease in a patient afflicted therewith comprising administering to said patient a therapeutically effective amount of a compound of claim 1 or 21.